STIC Search Report
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STIC Database Tracking Number: 152073

TO: Marcela Cordero Garcia **Location: 3c35 / 3c18** **Tuesday, May 03, 2005** **Art Unit: 1654** **Phone: 571-272-2939** **Serial Number: 10 / 611439**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Remsen 1a51** **Phone: 571-272-2504** **jan.delaval@uspto.gov**

Search Notes

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: MARCELA M CARDERO GARCIA Examiner # : 80381 Date: 4/29/05
Art Unit: 1654 Phone Number: 2-2939 Serial Number: 10/611,439
Location (Bldg/Room#): REM3C35 (Mailbox #): 3C18 Results Format Preferred (circle): PAPER DISK
****

MG

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: HYDROPHILIC BIOPOLYMER-DRUG CONJUGATES, THEIR PREPAR.

Inventors (please provide full names): SEE ATTACH'D BDS

Earliest Priority Date: 7/2/02

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

PLEASE SEARCH (A)

(A) → P-O-CH_2-CH_2-SO_2-$C(CH=CH_2)_n$, $n > 1$

wherein P = hyaluronan

AND CONJUGATE OF (A) + ALPHA INTERFERON

THANKS

****

STAFF USE ONLY

Searcher: am
Searcher Phone #: 22504
Searcher Location:
Date Searcher Picked Up: 5/3/05
Date Completed: 5/8/05
Searcher Prep & Review Time: 15
Online Time: 150

Type of Search

___ NA Sequence (#)
___ AA Sequence (#)
✓ Structure (#)
___ Bibliographic
___ Litigation
___ Fulltext
___ Other

Vendors and cost where applicable

✓ STN ___ Dialog
___ Questel/Orbit ___ Lexis/Nexis
___ Westlaw ___ WWW/Internet
___ In-house sequence systems
___ Commercial ___ Oligomer ___ Score/Length
___ Interference ___ SPDI ___ Encode/Transl
___ Other (specify)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 07:34:16 ON 03 MAY 2005
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STRUCTURE FILE UPDATES:     2 MAY 2005  HIGHEST RN 849658-68-0
DICTIONARY FILE UPDATES:    2 MAY 2005  HIGHEST RN 849658-68-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from  *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l11
L9                STR
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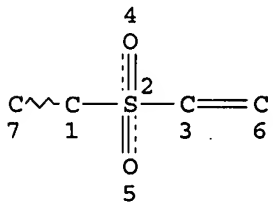


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   7

STEREO ATTRIBUTES: NONE
L11         3742 SEA FILE=REGISTRY SSS FUL L9

100.0% PROCESSED   6769 ITERATIONS                    3742 ANSWERS
SEARCH TIME: 00.00.01


=> d his
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     (FILE 'HOME' ENTERED AT 07:10:55 ON 03 MAY 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 07:11:54 ON 03 MAY 2005
L1             1 S US20040087488/PN OR (US2003-611439# OR US2002-393220#)/AP,PRN
               SEL RN

     FILE 'REGISTRY' ENTERED AT 07:13:35 ON 03 MAY 2005
L2            15 S E1-E15
L3             1 S 9004-61-9
L4             1 S 77-77-0
L5            13 S L2 NOT L3,L4
L6           680 S HYALURONAN OR HYALURONIC ACID
L7          1366 S ?HYALURON?/CNS
L8          1366 S L3,L6,L7
L9                STR
L10           50 S L9
L11         3742 S L9 FUL
               SAV L11 CORDERO611/A
L12          333 S 9004-61-9/CRN
L13         1368 S L8,L12
L14            1 S HYALURONIC ACID, SODIUM SALT/CN
L15           77 S 9067-32-7/CRN
L16         1368 S L13-L15
L17            5 S L11 AND L16
L18         1363 S L16 NOT L17
L19         3737 S L11 NOT L17

     FILE 'HCAPLUS' ENTERED AT 07:19:35 ON 03 MAY 2005
L20            5 S L17
L21        16945 S L18
L22        16520 S HYALURONIC ACID OR HYALURONAN OR (NA OR SODIUM)()HYALURON?
L23        20380 S L21,L22
L24         2717 S L19
L25          784 S DIVINYLSULFONE OR DIVINYLSULPHONE OR (DIVINYL OR DI VINYL)()(
L26         2924 S L24,L25
L27         6021 S HYALURONATE
L28        20802 S L23,L27
L29           36 S L26 AND L28
L30           55 S L28 AND (?VINYLSULFON? OR ?VINYLSULPHON? OR ?VINYL SULPHON? O
L31           57 S L29,L30
L32            3 S L31 AND ?INTERFERON?
               E INTERFERON/CT
L33        67394 S E3,E32+OLD,NT,PFT,RT
L34         1244 S E32-E52
L35        66650 S E88-E113
               E E33+ALL
L36          536 S E1,E2
               E INTERFERON/CT
               E E32+ALL
L37        67093 S E11+OLD,NT,PFT,RT
               E E27
L38        66650 S E3-E28
               E E3+ALL
L39        66951 S E6+OLD,NT
L40           39 S E8/BI
L41        82104 S E7/BI
L42            3 S L31 AND L33-L41
L43            3 S L32,L42
L44            1 S L43 AND (PARENT ? OR LARSEN ?)/AU
L45            1 S L43 AND GENZYM?/PA,CS
L46            1 S L1,L44,L45
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L47             2 S L43 NOT L46
                  SEL RN

     FILE 'REGISTRY' ENTERED AT 07:29:19 ON 03 MAY 2005
L48           135 S E1-E135
L49             2 S L48 AND L17-L19
L50             1 S L48 AND 25191-25-7
L51             1 S L48 AND 26101-52-0
L52            23 S L48 AND S/ELS
L53            20 S L52 NOT L49-L51

     FILE 'HCAPLUS' ENTERED AT 07:31:34 ON 03 MAY 2005
L54           928 S L50 OR L51
L55            41 S L54 AND L28
L56             1 S L55 AND L33-L41
L57             1 S L55 AND ?INTERFERON?
L58             3 S L43-L47,L56,L57
L59             0 S L20 AND ?INTERFERON?
L60             0 S L20 AND L33-L41
L61             0 S L20 AND ?CONJUGAT?
L62             0 S L20 AND CYTOKIN?
L63             8 S L20,L58 AND L1,L20-L47,L54-L62

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 07:34:37 ON 03 MAY 2005
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FILE COVERS 1907 - 3 May 2005  VOL 142 ISS 19
FILE LAST UPDATED: 2 May 2005  (20050502/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d l63 all hitstr tot

L63  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:372842  HCAPLUS
DN   140:368660
ED   Entered STN:  07 May 2004
TI   Preparation of hydrophilic biopolymer-drug conjugates as therapeutic
     agents
IN   Parent, Edward G.; Larsen, Nancy E.
PA   Genzyme Corporation, USA
SO   U.S. Pat. Appl. Publ., 6 pp.
     CODEN: USXXCO
DT   Patent
```

LA English
IC ICM A61K038-17
ICS A61K031-737; A61K031-716; C08B037-10; C08B037-00
INCL 514002000; 514054000; 514056000; 514057000; 530410000; 525054100; 525054200; 536021000; 536054000; 536084000
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004087488	A1	20040506	US 2003-611439	20030701 <--
PRAI US 2002-393220P	P	20020702 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004087488	ICM	A61K038-17
	ICS	A61K031-737; A61K031-716; C08B037-10; C08B037-00
	INCL	514002000; 514054000; 514056000; 514057000; 530410000; 525054100; 525054200; 536021000; 536054000; 536084000
US 2004087488	NCL	514/002.000; 514/054.000; 514/056.000; 514/057.000; 530/410.000; 525/054.100; 525/054.200; 536/021.000; 536/054.000; 536/084.000
	ECLA	A61K038/21A; A61K047/48K8 <--

AB Disclosed is preparation of a conjugate between a biol. active substance, such as an antineoplastic, an antibiotic, a protein, an enzyme or a peptide, with a **hyaluronan** or a mixture of a **hyaluronan** with at least one other hydrophilic polymer having a functional group capable of reacting with **divinylsulfone**. Also disclosed are stable intermediates formed by partially reacting a **hyaluronan** with **divinylsulfone** and stopping the reaction before completion to leave free, or reactive vinyl groups on the **hyaluronan** mol. available for conjugation with the biol. active substance. The thus formed conjugates are able to keep the biol. activity of the original active substance, and may be administered using pharmacol. acceptable carriers or vehicles. More specifically, the invention refers to conjugating α- **interferon** with a **hyaluronan** to treat neoplastic condition of an animal. For example, the conjugate between α- **interferon** and **hyaluronan** prepared by reacting 5.0μg **vinylsulfone** with 0.5g **hyaluronan** after being autoclaved for 20 min at 1210C to reduce the mol. weight, adding α- **interferon** for mixing in the cold for 18 h and dialyzing against 500 vols. of saline soln, was found to have the cytotoxicity against human pancreatic carcinoma cells.

ST hydrophilic biopolymer drug **vinylsulfone** conjugate prepn; **interferon hyaluronan vinylsulfone** conjugate antineoplastic

IT Antibodies and Immunoglobulins
RL: RCT (Reactant); RACT (Reactant or reagent)
(anti-bovine serum albumin; preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates, with **vinylsulfone**-activated **hyaluronan**; preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

IT Avidins
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

IT Antibiotics
(preparation of drug conjugates with **vinylsulfone**-activated

hyaluronan as antibiotics)
IT Antitumor agents
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan** as antineoplastics)
IT Dialysis
Physiological saline solutions
(purification of drug conjugates with **vinylsulfone**-activated **hyaluronan** by dialyzing with saline)
IT Avidins
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products with **vinylsulfone**-activated **hyaluronan**; preparation of drug conjugates with **vinylsulfone** -activated **hyaluronan**)
IT Glycosaminoglycans, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulfated, amino-; **vinylsulfone**-activated hydrophilic biopolymers capable of conjugating with drugs)
IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic, water soluble; **vinylsulfone**-activated hydrophilic biopolymers capable of conjugating with drugs)
IT Albumins, biological studies
Carbohydrates, biological studies
Collagens, biological studies
Elastins
Globulins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**vinylsulfone**-activated hydrophilic biopolymers capable of conjugating with drugs)
IT **Interferons**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(α , reaction products with **vinylsulfone** -activated **hyaluronan**; preparation of α - **interferon** conjugates with **vinylsulfone**-activated **hyaluronan**)
IT **Interferons**
RL: RCT (Reactant); RACT (Reactant or reagent)
(α ; preparation of α -**interferon** conjugates with **vinylsulfone**-activated **hyaluronan**)
IT 1403-66-3, Gentamicin 9002-04-4, Thrombin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug conjugates with **vinylsulfone**-activated **hyaluronan**)
IT **9004-61-9**, **Hyaluronan**
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); RCT (Reactant); PROC (Process); RACT (Reactant or reagent)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)
IT **77-77-0DP**, **Vinyl sulfone**, reaction products with **hyaluronan** and drugs 865-21-4DP, Vinblastin, reaction products with **vinylsulfone**-activated **hyaluronan** **9004-61-9DP**, **Hyaluronan**, reaction products with **vinylsulfone** and drugs 9007-43-6DP, Cytochrome C, reaction products with **vinylsulfone**-activated **hyaluronan** 33069-62-4DP, Paclitaxel, reaction products with **vinylsulfone** -activated **hyaluronan** 62229-50-9DP, Epidermal growth factor, reaction products with **vinylsulfone**-activated **hyaluronan**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

IT **77-77-0**, **Vinyl sulfone** 865-21-4, Vinblastin 9007-43-6, Cytochrome C, reactions 33069-62-4, Paclitaxel 62229-50-9, Epidermal growth factor
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

IT 9004-32-4, Carboxymethyl cellulose sodium salt 9004-62-0, Hydroxyethyl cellulose 9005-49-6, Heparin, biological studies 9007-28-7, Chondroitin sulfate 11138-66-2, Xanthan gum 169799-44-4, Keratin sulfate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**vinylsulfone**-activated hydrophilic biopolymers capable of conjugating with drugs)

IT 125935-84-4, Hylan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**vinylsulfone**-activated hylan capable of conjugating with drugs)

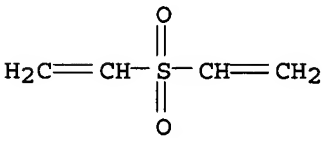
IT **9004-61-9**, **Hyaluronan**
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); RCT (Reactant); PROC (Process); RACT (Reactant or reagent)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **77-77-0DP**, **Vinyl sulfone**, reaction products with **hyaluronan** and drugs **9004-61-9DP**, **Hyaluronan**, reaction products with **vinylsulfone** and drugs
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

RN 77-77-0 HCAPLUS
CN Ethene, 1,1'-sulfonylbis- (9CI) (CA INDEX NAME)

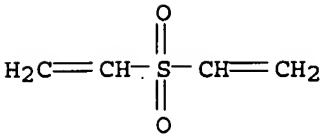


RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **77-77-0**, **Vinyl sulfone**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of drug conjugates with **vinylsulfone**-activated **hyaluronan**)

RN 77-77-0 HCAPLUS
CN Ethene, 1,1'-sulfonylbis- (9CI) (CA INDEX NAME)



L63 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:849373 HCAPLUS
DN 137:358081
ED Entered STN: 08 Nov 2002
TI Diagnostic imaging compositions, their methods of synthesis, and use
IN Li, Chun; Wen, Xiaoxia; Wu, Qing-Ping; Wallace, Sydney; Ellis, Lee M.
PA Board of Regents, the University of Texas System, USA
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 8
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002087498	A2	20021107	WO 2002-US12510	20020419
	WO 2002087498	A3	20031030		
	WO 2002087498	C1	20031211		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2444483	AA	20021107	CA 2002-2444483	20020419
	US 2002197261	A1	20021226	US 2002-126369	20020419
	US 2003003048	A1	20030102	US 2002-126216	20020419
	EP 1389090	A2	20040218	EP 2002-766783	20020419
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-286453P	P	20010426		
	US 2001-334969P	P	20011204		
	US 2001-343147P	P	20011220		
	WO 2002-US12510	W	20020419		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002087498	ICM	A61K
US 2002197261	NCL	424/178.100; 530/391.100
	ECLA	A61K047/48T6
US 2003003048	NCL	424/001.490; 530/391.100; 536/123.000; 530/350.000
	ECLA	A61K047/48R4; A61K047/48T6; A61K051/08Z; A61K051/10B28G; A61K051/10Z

AB Conjugate mols. comprising a ligand bonded to a polymer are disclosed. One such conjugate mol. comprises a ligand bonded to a polymer, a chelating agent bonded to the polymer, and a radioisotope chelated to the chelating agent. The conjugate mols. may be useful in detecting and/or treating tumors or biol. receptors. These conjugate mols. may be

synthesized without the necessity of preactivation of the ligand using an SCN-polymer-chelating agent precursor. Conjugate mols. incorporating an annexin V ligand are particularly useful for visualizing apoptotic cells. Conjugate mols. incorporating a C225 ligand are particularly useful for targeting tumors expressing EGFR.

ST indium 111 antibody annexin conjugate tumor imaging; immunoconjugate radiolabeled tumor targeting

IT Lymphoma
(B-cell; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Annexins
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(V, radiolabeled conjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Mammary gland, neoplasm
(adenocarcinoma; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Diagnosis
(agents; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to, radiolabeled; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Ischemia
(cerebral; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Intestine, neoplasm
(colon; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Apoptosis
(compns. comprising radiolabeled conjugates for imaging drug-induced apoptosis)

IT Antibodies and Immunoglobulins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(conjugates, radiolabeled; diagnostic imaging compns. comprising radiolabeled conjugates)

IT RGD peptides
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(cyclic, radiolabeled; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Bone, neoplasm
Brain, neoplasm
Drug delivery systems
Drug toxicity
Head, neoplasm
Human
Hypoxia, animal
Infection
Inflammation
Leukemia
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Multiple sclerosis
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Positron-emission tomography
Prostate gland, neoplasm
Radiopharmaceuticals
Regeneration, animal
Rheumatoid arthritis
Scintigraphy
Sickle cell anemia

Single-photon-emission computed tomography
Surgery
Thalassemia
Transplant rejection
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT Epidermal growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT Antibodies and Immunoglobulins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(fragments, radiolabeled conjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Drug delivery systems
(immunoconjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Drug delivery systems
(injections; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Reperfusion
(injury; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Brain, disease
(ischemia; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Antibodies and Immunoglobulins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(labeled; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Carcinoma
(mammary adenocarcinoma; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Dyes
(near-IR; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Neoplasm
(neck; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Neck, anatomical
(neoplasm; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Chelating agents
(radiolabeled conjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Amines, biological studies
Growth factors, animal
Hepatocyte growth factor
Interferons
Ligands
Peptides, biological studies
Phosphines
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polysaccharides, biological studies
Proteins
Thiols (organic), biological studies
Thrombospondins
Tumor necrosis factors
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(radiolabeled conjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Injury
(reperfusion; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Injury
(trauma; diagnostic imaging compns. comprising radiolabeled conjugates)

IT Imaging
(tumor; diagnostic imaging compns. comprising radiolabeled conjugates)
IT Reproductive tract, neoplasm
(vulva, squamous cell carcinoma; diagnostic imaging compns. comprising radiolabeled conjugates)
IT Carcinoma
(vulvar squamous cell; diagnostic imaging compns. comprising radiolabeled conjugates)
IT Integrins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(αvβ3, antibodies to, radiolabeled; diagnostic imaging compns. comprising radiolabeled conjugates)
IT 324740-00-3D, LM 609, radiolabeled conjugates
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(LM 609; diagnostic imaging compns. comprising radiolabeled conjugates)
IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to, radiolabeled; diagnostic imaging compns. comprising radiolabeled conjugates)
IT 147-94-4, Ara-c 33069-62-4, Paclitaxel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising radiolabeled conjugates for imaging drug-induced apoptosis)
IT 60-00-4D, EDTA, radiolabeled conjugates 295-37-4D, Cyclam, radiolabeled conjugates 365-08-2D, DTTP, radiolabeled conjugates 482-54-2D, 1,2-Cyclohexanediamine-N,N,N',N'-tetraacetic acid, radiolabeled conjugates 1429-50-1D, EDTMP, radiolabeled conjugates 2418-14-6D, Dimercaptosuccinic acid, radiolabeled conjugates 2809-21-4D, HEDP, radiolabeled conjugates 3565-84-2D, Cy-DTPA, radiolabeled conjugates 3599-32-4, Indocyanine green 9002-89-5D, Polyvinyl alcohol, radiolabeled conjugates 9003-01-4D, Polyacrylic acid, radiolabeled conjugates 9003-39-8D, Polyvinyl pyrrolidone, radiolabeled conjugates 9004-54-0D, Dextran, radiolabeled conjugates **9004-61-9D, Hyaluronic acid**, radiolabeled conjugates 9012-76-4D, Chitosan, radiolabeled conjugates 9044-05-7D, Carboxymethyl dextran, radiolabeled conjugates 10098-91-6D, Yttrium 90, radiolabeled conjugates, biological studies 13981-25-4D, Copper 64, radiolabeled conjugates, biological studies 14119-09-6D, Gallium 67, conjugates labeled with, biological studies 14344-48-0D, radiolabeled conjugates 14391-63-0D, Rubidium 82, conjugates labeled with, biological studies 14809-53-1D, Yttrium 86, radiolabeled conjugates, biological studies 15064-65-0D, Thallium 201, radiolabeled conjugates, biological studies 15735-70-3D, Platinum 193, radiolabeled conjugates, biological studies 15757-14-9D, Gallium 68, conjugates labeled with, biological studies 15757-86-5D, Copper 67, radiolabeled conjugates, biological studies 15827-60-8D, DTPMP, radiolabeled conjugates 25104-13-6D, Poly(D-glutamic acid), radiolabeled conjugates 25104-18-1D, Polylysine, radiolabeled conjugates 25322-69-4D, Polypropylene oxide, radiolabeled conjugates 25608-40-6D, Poly(L-aspartic acid), radiolabeled conjugates 26063-13-8D, Poly(L-aspartic acid), radiolabeled conjugates 27878-59-7D, Poly(2-hydroxyethyl L-glutamine), radiolabeled conjugates 27881-01-2D, Poly(D-aspartic acid), radiolabeled conjugates 27881-03-4D, Poly(DL-aspartic acid), radiolabeled conjugates 38000-06-5D, Polylysine, radiolabeled conjugates 49717-32-0D, radiolabeled conjugates 60239-18-1D, DOTA, radiolabeled conjugates 60239-20-5D, TRITA, radiolabeled conjugates 60239-22-7D, TETA, radiolabeled conjugates 62031-54-3D, FGF, radiolabeled conjugates 62229-50-9D, EGF, radiolabeled conjugates 72772-21-5D, radiolabeled conjugates 86090-08-6D, Angiostatin, radiolabeled conjugates 91987-74-5D, DOTP, radiolabeled conjugates 104162-48-3D, DOTMA, radiolabeled conjugates 113786-33-7D, BOPTA, radiolabeled conjugates 120041-08-9D, HP-DO3A, radiolabeled conjugates 120041-09-0D, radiolabeled conjugates 131418-52-5D,

radiolabeled conjugates 132446-35-6D, DOTMP, radiolabeled conjugates 133081-24-0D, 6-Hydrazinonicotinic acid, radiolabeled conjugates 136705-18-5D, DOTEP, radiolabeled conjugates 138149-64-1D, DOTPP, radiolabeled conjugates 145089-54-9D, DOTBzP, radiolabeled conjugates 158414-87-0D, Cy2-DTPA, radiolabeled conjugates 161167-43-7D, DOTPME, radiolabeled conjugates 174722-31-7D, Rituxan, radiolabeled conjugates 180288-69-1D, Herceptin, radiolabeled conjugates 186270-49-5D, Angiopoietin 1, radiolabeled conjugates 187888-07-9D, Endostatin, radiolabeled conjugates 194368-66-6D, Angiopoietin 2, radiolabeled conjugates 215369-21-4D, DC101, radiolabeled conjugates 221230-66-6D, radiolabeled conjugates 244082-19-7D, radiolabeled conjugates 474424-15-2D, radiolabeled conjugates
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT 67-43-6DP, DTPA, radiolabeled conjugates 15750-15-9DP, Indium 111, antibody conjugates labeled with, biological studies 25322-68-3DP, PEG, radiolabeled conjugates 205923-56-4DP, C225, radiolabeled conjugates
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT 24991-23-9D, paclitaxel conjugate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT **77-77-0, Vinyl sulfone** 122-04-3, p-Nitrobenzoyl chloride 541-59-3, Maleimide 23911-26-4, DTPA dianhydride 68181-17-9, SPDP 76931-93-6, N-Succinimidyl S-acetylthioacetate 198227-38-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT 474816-74-5P 474816-75-6P 474816-76-7P 474816-77-8P 474816-78-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT 474816-78-9DP, reaction products with annexin V
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(diagnostic imaging compns. comprising radiolabeled conjugates)

IT 477304-85-1P 477304-91-9P 477305-03-6P 477305-04-7P 477305-05-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in polymer immunoconjugate prepns. for tumor targeting)

IT 14133-76-7D, Technetium 99, radiolabeled conjugates, biological studies 14885-78-0D, Indium 113, radiolabeled conjugates, biological studies
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(metastable; diagnostic imaging compns. comprising radiolabeled conjugates)

IT 25513-46-6D, Poly-L-glutamic acid, paclitaxel conjugate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiolabeled conjugates; diagnostic imaging compns. comprising radiolabeled conjugates)

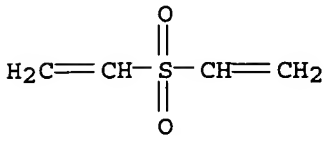
IT **9004-61-9D, Hyaluronic acid**, radiolabeled conjugates
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(diagnostic imaging compns. comprising radiolabeled conjugates)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **77-77-0, Vinyl sulfone**
RL: RCT (Reactant); RACT (Reactant or reagent)
(diagnostic imaging compns. comprising radiolabeled conjugates)

RN 77-77-0 HCAPLUS
CN Ethene, 1,1'-sulfonylbis- (9CI) (CA INDEX NAME)



L63 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:903929 HCAPLUS
DN 136:42844
ED Entered STN: 14 Dec 2001
TI Macromolecular drug complexes
IN Dadey, Eric J.; Zamiri, Camillia
PA The Board of Trustees of the University of Illinois, USA
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-30
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001093911	A2	20011213	WO 2001-US16163	20010517
	WO 2001093911	A3	20020307		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6417237	B1	20020709	US 2000-589721	20000608
	CA 2409268	AA	20011213	CA 2001-2409268	20010517
	EP 1286659	A2	20030305	EP 2001-937558	20010517
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001011506	A	20030624	BR 2001-11506	20010517
	JP 2003535149	T2	20031125	JP 2002-501482	20010517
	ZA 2002009229	A	20030807	ZA 2002-9229	20021113
PRAI	US 2000-589721	A	20000608		
	WO 2001-US16163	W	20010517		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001093911	ICM	A61K047-30
US 6417237	NCL	514/002.000; 424/085.500; 424/085.600; 424/085.700; 424/486.000; 424/487.000; 514/003.000; 514/012.000; 514/028.000; 514/062.000; 514/171.000; 514/805.000; 514/866.000; 514/938.000
	ECLA	A61K009/107D; A61K047/48K8; A61K047/48K4

AB Macromol. drug complexes containing a drug, like human growth hormone, and a polymer having a plurality of acid moieties, like carboxyl moieties or phosphonic acid moieties, and compns. containing the same, are disclosed. Compns., particularly microemulsions, containing the macromol. complexes are administered to individuals suffering from a disease or condition, and the

complexes release the drug (in vivo), to treat the disease or condition, and to reduce, eliminate, or reverse complications associated with the disease. An example complex was insulin with polyvinylphosphonic acid.

ST macromol drug complex

IT Amphiphiles
(macromol. drug complexes)

IT Peptides, biological studies
Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macromol. drug complexes)

IT Drug delivery systems
(microemulsions; macromol. drug complexes)

IT Vinyl compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymers; macromol. drug complexes)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α ; macromol. drug complexes)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β ; macromol. drug complexes)

IT **Interferons**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ ; macromol. drug complexes)

IT 9004-10-8, Insulin, biological studies
RL: FMU (Formation, unclassified); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(macromol. drug complexes)

IT 50-18-0, Cyclophosphamide 50-63-5, Chloroquine phosphate 52-67-5, Penicillamine 53-89-4, Benzpiperylon 54-85-3, Isoniazid 57-22-7, Vincristine 59-05-2, Methotrexate 114-07-8, Erythromycin 118-42-3, Hydroxychloroquine 865-21-4, Vinblastine 1405-87-4, Bacitracin 1406-11-7, Polymyxin 3416-24-8, Glucosamine 3615-24-5, Ramifenazone 9000-07-1, Carrageenan 9003-01-4, Polyacrylic acid **9004-61-9**, **Hyaluronic acid** 9005-11-2 9005-49-6, Heparin, biological studies 9007-28-7, Chondroitin sulfate 9007-92-5, Glucagon, biological studies 9056-36-4, Keratan sulfate 11075-36-8, Tuberactinomycin 12629-01-5, Human growth hormone 13539-59-8, Apazone 24967-94-0, Dermatan sulfate 25087-26-7, Polymethacrylic acid **25191-25-7**, Polyvinylsulfuric acid 26099-09-2, Polymaleic acid **26101-52-0**, **Polyvinylsulfonic** acid 27315-91-9, Pipebuzone 27754-99-0, Polyvinylphosphonic acid 28391-39-1, Poly(4-vinylbenzoic acid) 29098-15-5, Terofenamate 29382-27-2 32527-55-2, Tiaramide 50851-57-5, Polystyrenesulfonic acid 57132-53-3, Proglumetacin 57214-11-6 130139-10-5 165043-25-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macromol. drug complexes)

IT **9004-61-9**, **Hyaluronic acid 25191-25-7**, Polyvinylsulfuric acid **26101-52-0**, **Polyvinylsulfonic** acid
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macromol. drug complexes)

RN 9004-61-9 HCAPLUS

CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

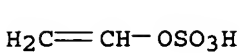
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25191-25-7 HCAPLUS

CN Sulfuric acid, monoethenyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

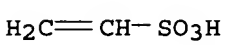
CRN 13401-80-4
CMF C2 H4 O4 S



RN 26101-52-0 HCAPLUS
CN Ethenesulfonic acid, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 1184-84-5
CMF C2 H4 O3 S



L63 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:576676 HCAPLUS
DN 131:186475
ED Entered STN: 14 Sep 1999
TI Process for producing crosslinked **hyaluronic acid**
IN Van Der Tuin, Everhardus; Besemer, Arie Cornelis
PA Stichting Hyppomedics, Neth.
SO Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C08B037-08
ICS A61L031-00
CC 44-5 (Industrial Carbohydrates)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 939086	A1	19990901	EP 1998-200620	19980227
	EP 939086	B1	20040310		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AT 261454	E	20040315	AT 1998-200620	19980227
	PT 939086	T	20040730	PT 1998-200620	19980227
	ES 2217496	T3	20041101	ES 1998-200620	19980227
PRAI	EP 1998-200620	A	19980227		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 939086	ICM	C08B037-08
	ICS	A61L031-00
EP 939086	ECLA	A61L031/04D+C08L5/08; C08B037/00P2F

AB A process for producing crosslinked **hyaluronic acid** (HA) or a salt thereof is disclosed, in which an aqueous solution of HA is crosslinked with **divinyl sulfone** (DVS) at a pH between 8 and 11 using a molar ratio of DVS/HA between 1 and 10%. The process results in a viscous aqueous solution of crosslinked **hyaluronic acid** or salt thereof, which is suitable for viscosupplementation of joints, especially for racing horses.
ST **divinyl sulfone** crosslinked **hyaluronic acid** viscosupplementation joint
IT Surgery
(orthopedic; process for producing crosslinked **hyaluronic acid**)
IT Joint, anatomical

(viscosupplements for; process for producing crosslinked **hyaluronic acid**)
IT **162975-50-0P, Divinyl sulfone-hyaluronic acid** copolymer
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for producing crosslinked **hyaluronic acid**)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Biomatrix Inc; GB 2151244 A 1985 HCAPLUS
(2) Biomatrix Inc; US 4582865 A 1986 HCAPLUS
IT **162975-50-0P, Divinyl sulfone-hyaluronic acid** copolymer
RL: IMF (Industrial manufacture); PREP (Preparation)
(process for producing crosslinked **hyaluronic acid**)
RN 162975-50-0 HCAPLUS
CN Hyaluronic acid, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

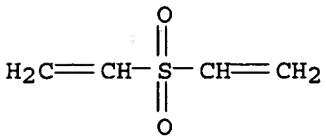
CM 1

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



L63 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:515629 HCAPLUS
DN 122:268527
ED Entered STN: 28 Apr 1995
TI Effect of preparation method on the hydration characteristics of hylan and comparison with another highly crosslinked polysaccharide, gum arabic
AU Takigami, Shoji; Takigami, Michiko; Phillips, Glyn O.
CS Dep. of Chemistry, Gunma Univ., Japan
SO Carbohydrate Polymers (1995), 26(1), 11-18
CODEN: CAPOD8; ISSN: 0144-8617
PB Elsevier
DT Journal
LA English
CC 44-7 (Industrial Carbohydrates)
AB The water binding characteristics of hylan are compared with gum arabic (I) using DSC. Both polysaccharide systems bind water effectively, and the transitions characteristic of two types of freezing-bound water can be distinguished from the melting or freezing of free water. There is evidence for the existence of metastable states of freezing-bound water within the two systems. I binds considerably less freezing-bound water than hylan systems. I does not have the same ability as **hyaluronic acid** to form structured entangled networks which can incorporate water within the matrix. The hylan samples are of

two types: hylan fluid where the **hyaluronan** chains are crosslinked with HCHO, and hylan gel where the crosslinking agent is **vinyl sulfone.** The hylan gel retains the freezing-bound state of water as a stable thermodn. state .apprx.20-50% more effectively than hylan prepared from the freeze-dried solid prepared from either concentrated or dilute hylan fluid. The traps formed from freeze-dried hylan gel are also more stable. Hylan gel prepared by precipitation with iso-PrOH and freeze-dried is the most effective hylan sample for stabilizing the freezing bound state. For this material even in .apprx.6% solution the vast majority of the water is retained in the freezing-bound form.

ST hylan hydration prepn effect; crosslinked **hyaluronic acid** hydration

IT Hydration, chemical
(effect of preparation method on the hydration characteristics of hylan)

IT 125935-84-4, Hylan **162975-49-7 162975-50-0**
RL: PRP (Properties)
(effect of preparation method on the hydration characteristics)

IT 9000-01-5, Gum arabic
RL: PRP (Properties)
(hydration characteristics)

IT **162975-49-7 162975-50-0**
RL: PRP (Properties)
(effect of preparation method on the hydration characteristics)

RN 162975-49-7 HCAPLUS

CN Hyaluronic acid, polymer with formaldehyde (9CI) (CA INDEX NAME)

CM 1

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 50-00-0
CMF C H2 O

$H_2C{=}O$

RN 162975-50-0 HCAPLUS

CN Hyaluronic acid, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

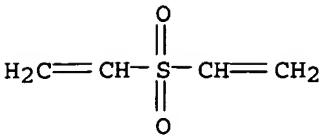
CM 1

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



L63 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:199228 HCAPLUS
DN 110:199228
ED Entered STN: 26 May 1989
TI Cross-linked **hyaluronate** gels for percutaneous embolization
IN Leshchiner, Adolf; Larsen, Nancy E.; Balazs, Endre A.; Hilal, Sadek K.
PA Biomatrix, Inc., USA
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K037-54
ICS A61K037-547
ICI A61K037-547, A61K037-54, A61K031-75, A61K031-725, A61K031-715
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 291177	A2	19881117	EP 1988-303395	19880414
	EP 291177	A3	19900307		
	EP 291177	B1	19920401		
	R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
	US 4795741	A	19890103	US 1987-47419	19870506
	AU 8814534	A1	19881110	AU 1988-14534	19880412
	AU 602973	B2	19901101		
	JP 03037950	B4	19910607	JP 1988-98049	19880420
	CA 1313617	A1	19930216	CA 1988-565368	19880428
PRAI	US 1987-47419	A	19870506		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 291177	ICM	A61K037-54
	ICS	A61K037-547
	ICI	A61K037-547, A61K037-54, A61K031-75, A61K031-725, A61K031-715
US 4795741	NCL	514/021.000; 514/781.000; 524/017.000; 524/027.000; 524/029.000; 536/004.100

AB A composition for blood vessel embolization comprises: a cross-linked gel of **hyaluronic acid** or hylan, or a mixed gel of **hyaluronic acid** or hylan co-crosslinked with other hydrophilic polymer(s); an organic quaternary ammonium compound; and thrombin. A gel containing 1 g Na hylan in 20 mL H2O was treated with 2.8 mL 2M NaOH, 10 g powdered Ta, 2 g H2O, and 0.2 g **vinyl sulfone** in 2 mL H2O and left to polymerize. The viscoelastic gel obtained was mixed with 0.06 g microcryst. cellulose and 0.1 g 20% hydroxymethylcellulose solution in normal saline, followed by autoclaving and addition of 2.5 NIH units thrombin to give a composition, which was mixed with 125I-labeled histamine. When injected into the ear artery of the rabbit, the composition formed an embolus, from which radioactivity was slowly released.

ST embolization gel polyhyaluronate; cancer treatment embolization gel; **hyaluronate** polymer embolization gel

IT Ion exchangers
(blood vessel-embolizing composition containing)

IT Radiography
(contrast media for, blood vessel-embolizing composition containing)

IT Neoplasm inhibitors
(embolization agents, polyhyaluronate-containing)
IT Embolism
(embolization, arterial, gel for, drug delivery and cancer treatment in relation to)
IT Pharmaceutical dosage forms
(gels, embolizing, polyhyaluronate-containing, cancer treatment in relation to)
IT 55-97-0 60-25-3, Hexamethonium chloride 60-31-1, Acetylcholine chloride 67-48-1, Choline chloride 1225-20-3, Sodium iothalamate 1403-66-3, Gentamicin 7225-61-8, Sodium metrizoate 7440-25-7, Tantalum, biological studies 7727-43-7, Barium sulfate 9002-04-4, Thrombin 9002-84-0, Polytetrafluoroethylene 9002-88-4, Polyethylene 9003-07-0 9004-34-6, Cellulose, biological studies **9004-61-9D**, **Hyaluronic acid**, crosslinked 9011-04-5, Hexadimethrine bromide 9012-36-6, Agarose 28728-55-4, Hexadimethrine bromide 31112-62-6, Metrizamide 52219-08-6, Sephadex QAE **105524-32-1**
RL: BIOL (Biological study)
(blood vessel-embolizing composition containing)
IT **9004-61-9D**, **Hyaluronic acid**, crosslinked
105524-32-1
RL: BIOL (Biological study)
(blood vessel-embolizing composition containing)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 105524-32-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

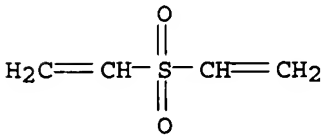
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



L63 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:605193 HCAPLUS
DN 107:205193
ED Entered STN: 27 Nov 1987
TI Drug delivery systems based on **hyaluronan**, derivatives thereof and their salts and method of producing same
IN Balazs, Endre A.; Larsen, Nancy E.; Leshchiner, Adolf
PA Biomatrix, Inc., USA
SO Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW

DT Patent
LA English
IC ICM A61K047-00
ICS A61L015-03
CC 63-6 (Pharmaceuticals)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 224987	A2	19870610	EP 1986-306046	19860805
	EP 224987	A3	19871119		
	EP 224987	B1	19920415		
	R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
	AU 8660903	A1	19870604	AU 1986-60903	19860805
	AU 595524	B2	19900405		
	CA 1340199	A1	19981215	CA 1986-516770	19860825
	JP 62129226	A2	19870611	JP 1986-219096	19860916
	JP 06092320	B4	19941116		
PRAI	US 1985-804178	A	19851129		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 224987	ICM	A61K047-00
	ICS	A61L015-03

AB **Hyaluronic acid** and its derivs. are used for sustained-release of pharmaceutical substances. It may be crosslinked with **divinyl sulfone**, or may be a viscoelastic putty. It is useful for topical products such as eye drops. **Na hyaluronate** 0.58 g was swelled with water 20 mL for 20 h and treated with aqueous NaOH and crosslinked with **divinylsulfone**. The gel was placed in an NaCl-phosphate buffer and dialyzed against 0.15 M NaCl for 5 days. The crosslinked **hyaluronic acid** concentration was 0.21%; this gel was mixed with mydriacyl to a concentration of 0.5%. Rabbits treated with this mydriacyl-**hyaluronic acid** composition maintained a >50% pupil size increase for .apprx.340 min., compared to 240 min. for controls treated with mydriacyl in salts solution The role of pupil size decrease was also slower in test rabbits, indicating the combination of a drug with **hyaluronic acid** gel significantly prolonged the period of effectiveness of the drug.

ST **hyaluronate** sustained drug release

IT Urethane polymers, biological studies
RL: BIOL (Biological study)
(sponge, drug delivery system containing, as support)

IT Medical goods
(dressings, **hyaluronate** gel-immobilized gauge in, for sustained-release)

IT Pharmaceutical dosage forms
(eye solns., sustained-release, **hyaluronates** in)

IT Pharmaceutical dosage forms
(topical, **hyaluronates** in)

IT Pharmaceutical dosage forms
(transdermal, sustained-release, **hyaluronates** in)

IT **105524-32-1DP**, reaction products with gentamicin **105524-32-1P 111307-33-6P**
RL: PREP (Preparation)
(preparation of, for sustained drug release system)

IT 1403-66-3DP, Gentamycin, reaction products with **sodium hyaluronate-divinylsulfone** copolymer
RL: PREP (Preparation)
(preparation of, for sustained-release)

IT 50-67-9, Serotonin, biological studies 69-72-7, biological studies
RL: BIOL (Biological study)
(sustained release delivery of, **hyaluronan** for)

IT 1508-75-4
RL: BIOL (Biological study)
(sustained release delivery of, hyaluronante-**divinylsulfone** copolymer for)
IT 1403-66-3
RL: BIOL (Biological study)
(sustained-release delivery of, **hyaluronates** in)
IT **9004-61-9**, **Hyaluronic acid 9067-32-7**
, **Sodium hyaluronate**
RL: BIOL (Biological study)
(sustained-release drug delivery system containing)
IT **105524-32-1DP**, reaction products with gentamicin
105524-32-1P 111307-33-6P
RL: PREP (Preparation)
(preparation of, for sustained drug release system)
RN 105524-32-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

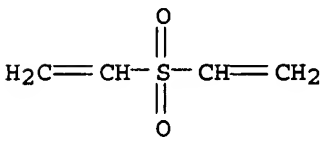
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



RN 105524-32-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

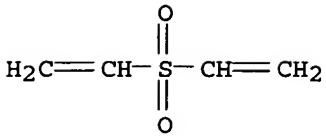
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



RN 111307-33-6 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with chondroitin hydrogen sulfate and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

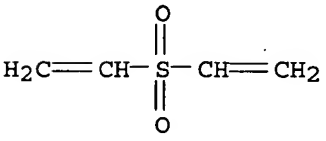
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



CM 3

CRN 9007-28-7
CMF H2 O4 S . x Unspecified

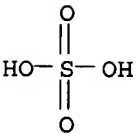
CM 4

CRN 9007-27-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 7664-93-9
CMF H2 O4 S



IT **9004-61-9, Hyaluronic acid 9067-32-7 , Sodium hyaluronate**
RL: BIOL (Biological study)

(sustained-release drug delivery system containing)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9067-32-7 HCAPLUS
CN Hyaluronic acid, sodium salt (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L63 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1986:632207 HCAPLUS
DN 105:232207
ED Entered STN: 26 Dec 1986
TI Crosslinked gels of **hyaluronic acid** and products containing these gels for cosmetics and pharmaceuticals
IN Balazs, Endre A.; Leshchiner, Adolf
PA Biomatrix, Inc., USA
SO U.S., 10 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C08F008-00
INCL 524029000
CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4582865	A	19860415	US 1984-678895	19841206
	US 4636524	A	19870113	US 1985-709977	19850308
	CA 1230186	A1	19871208	CA 1985-481055	19850508
	GB 2168067	A1	19860611	GB 1985-12072	19850513
	GB 2168067	B2	19890607		
	AU 8543045	A1	19860612	AU 1985-43045	19850528
	AU 569157	B2	19880121		
	FR 2574414	A1	19860613	FR 1985-7941	19850528
	FR 2574414	B1	19870703		
	DE 3520008	A1	19860619	DE 1985-3520008	19850604
	DE 3520008	C2	19911010		
	JP 61138601	A2	19860626	JP 1985-147612	19850704
	JP 04030961	B4	19920525		
	SE 8503486	A	19860607	SE 1985-3486	19850715
	SE 460792	B	19891120		
	SE 460792	C	19900315		
	US 4605691	A	19860812	US 1985-755976	19850718
	GB 2181147	A1	19870415	GB 1986-18719	19860731
	GB 2181147	B2	19890607		
	GB 2181148	A1	19870415	GB 1986-18720	19860731
	GB 2181148	B2	19890607		
	AU 8772173	A1	19870827	AU 1987-72173	19870428
	AU 572419	B2	19880505		
	GB 2205848	A1	19881221	GB 1988-17772	19880726
	GB 2205848	B2	19890524		
	SE 8901672	A	19890510	SE 1989-1672	19890510
	SE 501828	C2	19950522		
	JP 02138346	A2	19900528	JP 1989-232667	19890906
	JP 06037575	B4	19940518		
	US 5128326	A	19920707	US 1990-559413	19900723
PRAI	US 1984-678895	A3	19841206		
	US 1985-709977	A2	19850308		
	GB 1985-12072	A3	19850513		
	US 1985-755976	A2	19850718		

US 1985-804178 B1 19851129
US 1988-140877 B1 19880106
US 1989-320822 B1 19890309

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 4582865	ICM	C08F008-00
	INCL	524029000
US 4582865	NCL	524/029.000; 514/781.000; 524/027.000; 536/004.100
US 4636524	NCL	514/781.000
US 4605691	NCL	524/027.000; 524/029.000; 536/004.100
US 5128326	NCL	514/054.000; 424/446.000; 514/769.000

AB Mixed crosslinked gels of **hyaluronic acid** and ≥1 other hydrophilic polymer having a functional group capable of reacting with **divinyl sulfone** is prepared by subjecting a mixture of **Na hyaluronate** and the other hydrophilic polymer in a dilute aqueous alkaline solution at a pH ≥9 to a crosslinking reaction with **divinyl sulfone** at .apprx.20°. The gels may contain an inert water-insol. substance, e.g., a hydrocarbon, an oil or fat, a pigment, polyethylene, or poly(tetrafluoroethylene), or covalently bonded low mol. weight substances such as drugs, especially carminic acid. These products are useful in cosmetic formulations and as drug delivery systems. Thus, a cosmetic formulation contained crosslinked gel 90, Hyloderm (1% solution of **Na hyaluronate**) 5, and Polyox 1% solution 5% by weight, had the appearance of a homogeneous viscous liquid, and it gave a soft, silky feel when applied to the skin.

ST **hyaluronate** gel cosmetic pharmaceutical

IT Albumins
Collagens, biological studies
Elastins
Globulins
RL: BIOL (Biological study)
(cosmetic and pharmaceutical gels from **hyaluronic acid** and **divinyl sulfone** and)

IT Pharmaceuticals
(delivery systems, gels from **hyaluronic acid** and hydrophilic polymers and **divinyl sulfone** as)

IT Beeswax
Coconut oil
Kaolin, biological studies
Lanolin
Petrolatum
RL: BIOL (Biological study)
(**hyaluronate** mixed crosslinked gel containing, for cosmetics)

IT Polymers, biological studies
RL: BIOL (Biological study)
(hydrophilic, cosmetic and pharmaceutical gels from **hyaluronic acid** and **divinyl sulfone** and)

IT Cosmetics
(gels, from **hyaluronic acid** and hydrophilic polymers and **divinyl sulfone**)

IT Mucopolysaccharides, compounds
RL: BIOL (Biological study)
(glycosaminoglycans, sulfated, cosmetic and pharmaceutical gels from **hyaluronic acid** and **divinyl sulfone** and)

IT **105524-26-3 105524-27-4 105524-32-1D**, reaction products with collagen
RL: BIOL (Biological study)
(as cosmetic and pharmaceutical gel network for water-insol. substances)

IT 9004-62-0 9005-49-6, biological studies 9007-28-7 9056-36-4 11138-66-2

RL: BIOL (Biological study)
(cosmetic and pharmaceutical gels from **hyaluronic acid** and **divinyl sulfone** and)

IT **9004-61-9**
RL: BIOL (Biological study)
(cosmetic and pharmaceutical gels from hydrophilic polymers and **divinyl sulfone** and)

IT **105524-28-5P 105524-29-6P 105524-30-9P 105524-31-0P 105524-32-1P**
RL: PREP (Preparation)
(gel, preparation and swelling ratio of)

IT 1260-17-9 9002-84-0 9002-88-4
RL: BIOL (Biological study)
(**hyaluronate** mixed crosslinked gel containing)

IT 1309-37-1, biological studies
RL: BIOL (Biological study)
(**hyaluronate** mixed crosslinked gel containing, for cosmetics)

IT **105524-26-3 105524-27-4 105524-32-1D**, reaction products with collagen
RL: BIOL (Biological study)
(as cosmetic and pharmaceutical gel network for water-insol. substances)

RN 105524-26-3 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with heparin and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

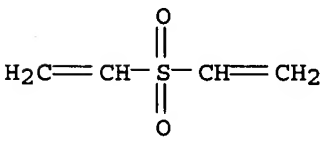
CM 2

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 77-77-0
CMF C4 H6 O2 S



RN 105524-27-4 HCAPLUS
CN Cellulose, carboxymethyl ether, sodium salt, polymer with hyaluronic acid sodium salt and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

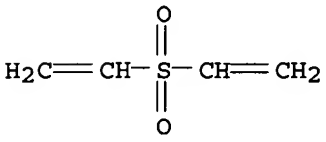
CRN 9067-32-7
CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



CM 3

CRN 9004-32-4
CMF C2 H4 O3 . x Na . x Unspecified

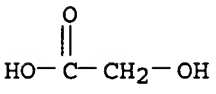
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 79-14-1
CMF C2 H4 O3



RN 105524-32-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

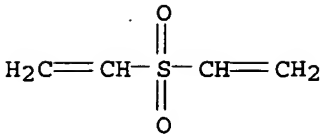
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S

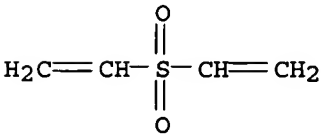


IT **9004-61-9**
RL: BIOL (Biological study)
(cosmetic and pharmaceutical gels from hydrophilic polymers and **divinyl sulfone** and)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **105524-28-5P 105524-29-6P 105524-30-9P**
105524-31-0P 105524-32-1P
RL: PREP (Preparation)
(gel, preparation and swelling ratio of)
RN 105524-28-5 HCAPLUS
CN Cellulose, carboxymethyl ether, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

CRN 9004-32-4
CMF C2 H4 O3 . x Na . x Unspecified

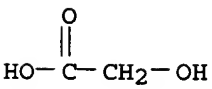
CM 3

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 79-14-1
CMF C2 H4 O3

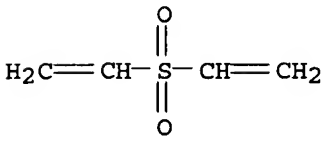


RN 105524-29-6 HCAPLUS

CN Cellulose, 2-hydroxyethyl 2-[2-hydroxy-3-(trimethylammonio)propoxy]ethyl 2-hydroxy-3-(trimethylammonio)propyl ether, chloride, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

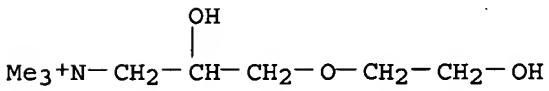
CRN 81859-24-7
CMF C8 H20 N O3 . x C6 H16 N O2 . x C2 H6 O2 . x Cl . x Unspecified

CM 3

CRN 170553-71-6
CMF C8 H20 N O3 . x C6 H16 N O2 . x C2 H6 O2 . x Unspecified

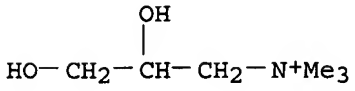
CM 4

CRN 170344-46-4
CMF C8 H20 N O3



CM 5

CRN 44814-66-6
CMF C6 H16 N O2



CM 6

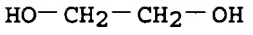
CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 7

CRN 107-21-1

CMF C2 H6 O2



RN 105524-30-9 HCAPLUS
CN Xanthan gum, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

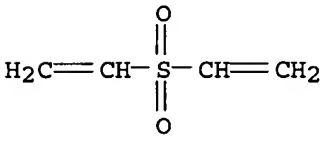
CM 1

CRN 11138-66-2
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

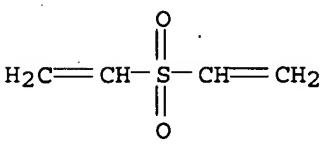
CRN 77-77-0
CMF C4 H6 O2 S



RN 105524-31-0 HCAPLUS
CN Cellulose, 2-hydroxyethyl ether, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

CRN 9004-62-0
CMF C2 H6 O2 . x Unspecified

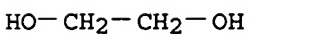
CM 3

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 107-21-1
CMF C2 H6 O2



RN 105524-32-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

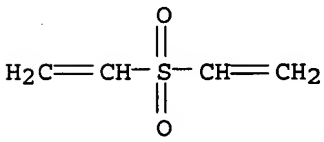
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



=> sel hit rn l63
E136 THROUGH E150 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 07:35:13 ON 03 MAY 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 2 MAY 2005 HIGHEST RN 849658-68-0
DICTIONARY FILE UPDATES: 2 MAY 2005 HIGHEST RN 849658-68-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *

****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> => d his l64-

(FILE 'HCAPLUS' ENTERED AT 07:31:34 ON 03 MAY 2005)

FILE 'REGISTRY' ENTERED AT 07:34:16 ON 03 MAY 2005

FILE 'HCAPLUS' ENTERED AT 07:34:37 ON 03 MAY 2005
SEL HIT RN L63

FILE 'REGISTRY' ENTERED AT 07:35:13 ON 03 MAY 2005
L64 15 S E136-E150
L65 5 S L64 AND L17
L66 3 S L64 AND L16 NOT L65
L67 7 S L64 NOT L65,L66

=> d ide can tot l65

L65 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2005 ACS on STN
RN **162975-50-0** REGISTRY
ED Entered STN: 12 May 1995
CN **Hyaluronic acid, polymer with 1,1'-sulfonylbis[ethene] (9CI)**
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Ethene, 1,1'-sulfonylbis-, polymer with hyaluronic acid (9CI)**
OTHER NAMES:
CN **Divinyl sulfone-hyaluronic acid copolymer**
MF (C4 H6 O2 S . Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS

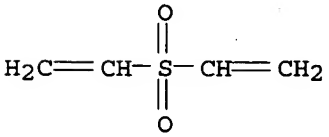
CM 1

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



2 REFERENCES IN FILE CA (1907 TO DATE)

2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 131:186475

REFERENCE 2: 122:268527

L65 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2005 ACS on STN
RN **111307-33-6** REGISTRY
ED Entered STN: 14 Nov 1987
CN **Hyaluronic acid, sodium salt, polymer with chondroitin hydrogen sulfate and 1,1'-sulfonylbis[ethene] (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Chondroitin, hydrogen sulfate, polymer with hyaluronic acid sodium salt and 1,1'-sulfonylbis[ethene] (9CI)**
CN **Ethene, 1,1'-sulfonylbis-, polymer with chondroitin hydrogen sulfate and hyaluronic acid sodium salt (9CI)**
MF (C4 H6 O2 S . H2 O4 S . x Unspecified . Unspecified)x
CI PMS
PCT Manual component, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS

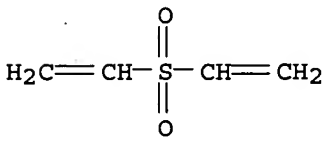
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



CM 3

CRN 9007-28-7
CMF H2 O4 S . x Unspecified

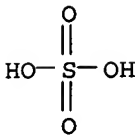
CM 4

CRN 9007-27-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 7664-93-9
CMF H2 O4 S



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 107:205193

L65 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-32-1** REGISTRY
ED Entered STN: 06 Dec 1986
CN **Hyaluronic acid, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Ethene, 1,1'-sulfonylbis-, polymer with hyaluronic acid sodium salt (9CI)**
MF (C4 H6 O2 S . Unspecified)x
CI PMS
PCT Manual component, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

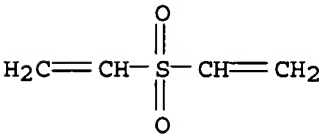
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



3 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 110:199228

REFERENCE 2: 107:205193

REFERENCE 3: 105:232207

L65 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-27-4** REGISTRY
ED Entered STN: 06 Dec 1986
CN **Cellulose, carboxymethyl ether, sodium salt, polymer with hyaluronic acid sodium salt and 1,1'-sulfonylbis[ethene] (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN **Ethene, 1,1'-sulfonylbis-, polymer with cellulose carboxymethyl ether sodium salt and hyaluronic acid sodium salt (9CI)**
CN **Hyaluronic acid, sodium salt, polymer with cellulose carboxymethyl ether sodium salt and 1,1'-sulfonylbis[ethene] (9CI)**
MF (C4 H6 O2 S . C2 H4 O3 . x Na . x Unspecified . Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

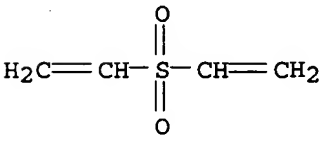
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



CM 3

CRN 9004-32-4
CMF C2 H4 O3 . x Na . x Unspecified

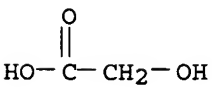
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 79-14-1
CMF C2 H4 O3



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 105:232207

L65 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-26-3** REGISTRY

ED Entered STN: 06 Dec 1986
CN **Hyaluronic acid, sodium salt, polymer with heparin and 1,1'-sulfonylbis[ethene] (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Ethene, 1,1'-sulfonylbis-, polymer with heparin and hyaluronic acid sodium salt (9CI)**
CN **Heparin, polymer with hyaluronic acid sodium salt and 1,1'-sulfonylbis[ethene] (9CI)**
MF (C4 H6 O2 S . Unspecified . Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

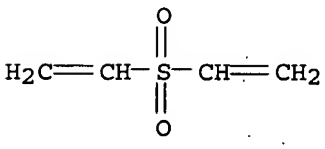
CM 2

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 77-77-0
CMF C4 H6 O2 S



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 105:232207

=> d ide can tot 166

L66 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **162975-49-7** REGISTRY
ED Entered STN: 12 May 1995
CN **Hyaluronic acid, polymer with formaldehyde (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Formaldehyde, polymer with hyaluronic acid (9CI)**
MF (C H2 O . Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyether, Polyether formed
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 50-00-0
CMF C H2 O

$H_2C{=}O$

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 122:268527

L66 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9067-32-7** REGISTRY
ED Entered STN: 16 Nov 1984
CN **Hyaluronic acid, sodium salt (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Artz
CN Artz Dispo
CN Artzal
CN Bio Hyaluro 12
CN **Chlamyhyaluronic acid sodium salt**
CN Eashave
CN FCH 200
CN FCH 248
CN HA-F
CN HA-Q
CN HA-Q 1
CN HA-QA
CN Healon
CN Healon (polysaccharide)
CN Healon GV
CN Healon V
CN Hyalart
CN Hyalein
CN Hyalgan
CN Hyasol
CN Hyladerm
CN Nidelon
CN NRD 101
CN Opegan
CN Orthovisc
CN Provisc
CN SI 4402
CN SL 1010
CN SLM 10
CN **Sodium hyaluronate**
CN SPH
DR 34448-35-6
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyother, Polyother only

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
1750 REFERENCES IN FILE CA (1907 TO DATE)
75 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1753 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:360893

REFERENCE 2: 142:360870

REFERENCE 3: 142:360869

REFERENCE 4: 142:341916

REFERENCE 5: 142:341871

REFERENCE 6: 142:337729

REFERENCE 7: 142:329311

REFERENCE 8: 142:322755

REFERENCE 9: 142:322536

REFERENCE 10: 142:303681

L66 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9004-61-9** REGISTRY
ED Entered STN: 16 Nov 1984
CN **Hyaluronic acid (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN ACP
CN ACP (polysaccharide)
CN ACP gel
CN **Chlamyhyaluronic acid**
CN Durolane
CN Genzyme 9983
CN HA 9
CN Hy 20
CN Hyalobarrier gel
CN Hyalofill
CN **Hyaluronan**
CN **Hyaluronsan HA-F**
CN Hylan G-F 20
CN Hylartil
CN Luronit
CN Mucoitin
CN Sepracoat
CN Sofast
CN Synvisc
DR 165324-65-2, 9039-38-7, 37243-73-5, 29382-75-0
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyester, Polyester formed
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*,

IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PATDPASPC, PHAR, PIRA, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11920 REFERENCES IN FILE CA (1907 TO DATE)
966 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11944 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:360934

REFERENCE 2: 142:360870

REFERENCE 3: 142:360869

REFERENCE 4: 142:360724

REFERENCE 5: 142:360694

REFERENCE 6: 142:360659

REFERENCE 7: 142:360482

REFERENCE 8: 142:360452

REFERENCE 9: 142:360340

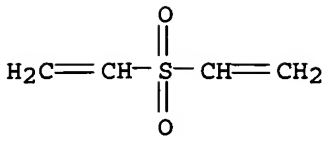
REFERENCE 10: 142:356757

=> d ide can tot l67

L67 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-31-0** REGISTRY
ED Entered STN: 06 Dec 1986
CN Cellulose, 2-hydroxyethyl ether, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethene, 1,1'-sulfonylbis-, polymer with cellulose 2-hydroxyethyl ether (9CI)
OTHER NAMES:
CN Divinyl sulfone-hydroxyethyl cellulose copolymer
DR 173523-81-4
MF (C4 H6 O2 S . C2 H6 O2 . x Unspecified)x
CI PMS
PCT Manual component, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

CRN 9004-62-0
CMF C2 H6 O2 . x Unspecified

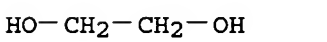
CM 3

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 107-21-1
CMF C2 H6 O2



5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:397095

REFERENCE 2: 124:179201

REFERENCE 3: 124:148199

REFERENCE 4: 113:233535

REFERENCE 5: 105:232207

L67 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-30-9** REGISTRY
ED Entered STN: 06 Dec 1986
CN Xanthan gum, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethene, 1,1'-sulfonylbis-, polymer with xanthan gum (9CI)
MF (C4 H6 O2 S . Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

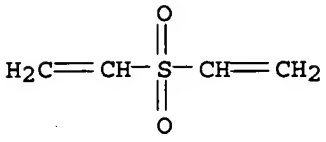
CM 1

CRN 11138-66-2
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0
CMF C4 H6 O2 S



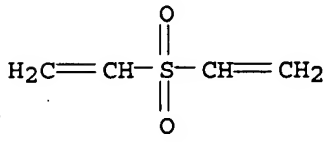
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 105:232207

L67 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-29-6** REGISTRY
ED Entered STN: 06 Dec 1986
CN Cellulose, 2-hydroxyethyl 2-[2-hydroxy-3-(trimethylammonio)propoxy]ethyl 2-hydroxy-3-(trimethylammonio)propyl ether, chloride, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethene, 1,1'-sulfonylbis-, polymer with cellulose 2-hydroxyethyl 2-[2-hydroxy-3-(trimethylammonio)propoxy]ethyl 2-hydroxy-3-(trimethylammonio)propyl ether chloride (9CI)
MF (C8 H20 N O3 . x C6 H16 N O2 . C4 H6 O2 S . x C2 H6 O2 . x Cl . x Unspecified)x
CI PMS
PCT Manual component, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

CRN 81859-24-7
CMF C8 H20 N O3 . x C6 H16 N O2 . x C2 H6 O2 . x Cl . x Unspecified

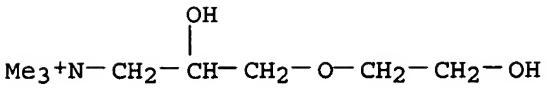
CM 3

CRN 170553-71-6
CMF C8 H20 N O3 . x C6 H16 N O2 . x C2 H6 O2 . x Unspecified

CM 4

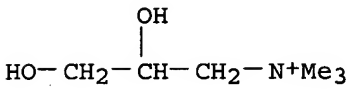
CRN 170344-46-4

CMF C8 H20 N O3



CM 5

CRN 44814-66-6
CMF C6 H16 N O2



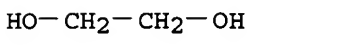
CM 6

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 7

CRN 107-21-1
CMF C2 H6 O2



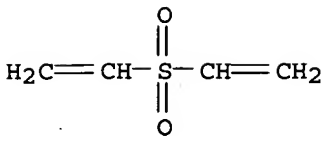
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 105:232207

L67 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **105524-28-5** REGISTRY
ED Entered STN: 06 Dec 1986
CN Cellulose, carboxymethyl ether, sodium salt, polymer with 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethene, 1,1'-sulfonylbis-, polymer with cellulose carboxymethyl ether, sodium salt (9CI)
OTHER NAMES:
CN Carboxymethyl cellulose sodium salt-divinyl sulfone copolymer
MF (C4 H6 O2 S . C2 H4 O3 . x Na . x Unspecified)x
CI PMS
PCT Manual component, Polyester, Polyester formed, Polyother, Polyvinyl
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 77-77-0
CMF C4 H6 O2 S



CM 2

CRN 9004-32-4
CMF C2 H4 O3 . x Na . x Unspecified

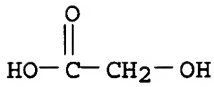
CM 3

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 79-14-1
CMF C2 H4 O3



4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:397095

REFERENCE 2: 124:179201

REFERENCE 3: 113:233535

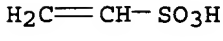
REFERENCE 4: 105:232207

L67 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **26101-52-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN Ethenesulfonic acid, homopolymer (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethenesulfonic acid, polymers (8CI)
OTHER NAMES:
CN Ethylenesulfonic acid polymer
CN Poly(ethenesulfonic acid)
CN Poly(ethylenesulfonic acid)
CN Poly(vinylsulfonic acid)
CN PVS
CN Vinylsulfonic acid homopolymer
CN Vinylsulfonic acid polymer
MF (C2 H4 O3 S)x
CI PMS, COM
PCT Polyvinyl
LC STN Files: AGRICOLA, BIOSIS, CA, CAPLUS, IFICDB, IFIPAT, IFIUDB,

MEDLINE, PHAR, PIRA, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL

CM 1

CRN 1184-84-5
CMF C2 H4 O3 S



598 REFERENCES IN FILE CA (1907 TO DATE)
49 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
600 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:361384

REFERENCE 2: 142:345186

REFERENCE 3: 142:330269

REFERENCE 4: 142:325965

REFERENCE 5: 142:308667

REFERENCE 6: 142:288942

REFERENCE 7: 142:288940

REFERENCE 8: 142:281226

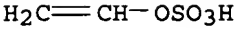
REFERENCE 9: 142:276448

REFERENCE 10: 142:270705

L67 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **25191-25-7** REGISTRY
ED Entered STN: 16 Nov 1984
CN Sulfuric acid, monoethenyl ester, homopolymer (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Sulfuric acid, monovinyl ester, polymers (8CI)
OTHER NAMES:
CN Poly(monovinyl sulfate)
CN Poly(vinyl sulfate)
CN Poly(vinyl sulfuric acid)
CN PVS
CN Vinyl sulfate polymers
MF (C2 H4 O4 S)x
CI PMS, COM
PCT Polyvinyl
LC STN Files: ANABSTR, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PIRA, TOXCENTER, USPAT2, USPATFULL
Other Sources: NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 13401-80-4
CMF C2 H4 O4 S



381 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
382 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:332038

REFERENCE 2: 142:310567

REFERENCE 3: 142:293922

REFERENCE 4: 142:222098

REFERENCE 5: 142:193800

REFERENCE 6: 142:182186

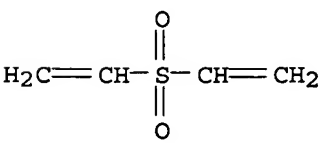
REFERENCE 7: 142:101067

REFERENCE 8: 142:79723

REFERENCE 9: 141:427885

REFERENCE 10: 141:427662

L67 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN **77-77-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN Ethene, 1,1'-sulfonylbis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Vinyl sulfone (6CI, 8CI)
OTHER NAMES:
CN Bis(ethenyl)sulfone
CN Divinyl sulfone
CN NSC 133793
CN NSC 18590
CN NSC 57304
FS 3D CONCORD
MF C4 H6 O2 S
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DETHERM*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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            727 REFERENCES IN FILE CA (1907 TO DATE)
             82 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            730 REFERENCES IN FILE CAPLUS (1907 TO DATE)
             44 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE   1:  142:355332

REFERENCE   2:  142:340744

REFERENCE   3:  142:266540

REFERENCE   4:  142:264348

REFERENCE   5:  142:245993

REFERENCE   6:  142:245840

REFERENCE   7:  142:204919

REFERENCE   8:  142:204857

REFERENCE   9:  142:201620

REFERENCE  10:  142:179164


=> => fil wpix
FILE 'WPIX' ENTERED AT 07:56:45 ON 03 MAY 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED:          27 APR 2005     <20050427/UP>
MOST RECENT DERWENT UPDATE:     200527       <200527/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

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    PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
    FOR DETAILS. <<<

=> d his l68-

     (FILE 'REGISTRY' ENTERED AT 07:35:13 ON 03 MAY 2005)

     FILE 'WPIX' ENTERED AT 07:36:46 ON 03 MAY 2005
L68         3943 S L22/BIX OR L27/BIX
L69         4508 S ?HYALURON?/BIX
                 E HYALURON/DCN
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                E E4+ALL
L70          2038 S E2 OR R03231/PLE
L71          1391 S E4
                E HYALURON/CN
L72            13 S E4-E29
                SEL SDCN
                EDIT /SDCN DCN
L73           349 S (RAB0IN OR RA26F9 OR RA1VXB OR RA08TA OR RA08T8 OR RA121P OR
L74             2 S (RABOIN OR RAO8TA OR RAO8T8 OR RAO31D OR RAOQBE OR RAOKTS OR
L75          4793 S L68-L71,L73,L74
L76          2064 S (C08B037-08 OR C08L005-08 OR C09D105-08 OR C09J105-08)/IPC
L77          6433 S L75,L76
L78           485 S C08B037-10/IPC
L79          8422 S C08B037/IPC
L80         15620 S C08B/IPC
L81           255 S L25/BIX
L82          3702 S (?VINYLSULFON? OR ?VINYLSULPHON? OR ?VINYL SULFON? OR ?VINYL
                E DIVINYL SULFONE/DCN
                E E11+ALL
L83            47 S E2
L84          3710 S L81-L83
L85            58 S L84 AND L77
L86             1 S L84 AND L78
L87            49 S L84 AND L79
L88            84 S L84 AND L80
L89           127 S L85-L88
L90             4 S L89 AND ?INTERFERON?/BIX
L91             0 S L89 AND PLAFERON?/BIX
L92             4 S L89 AND (B02-V03 OR C02-V03 OR B04-H05? OR C04-H05? OR B14-G0
L93             5 S L90,L92
L94             4 S L89 AND (PARENT ? OR LARSEN ?)/AU
L95             2 S L89 AND GENZYM?/PA
L96             5 S L94,L95
L97             9 S L93,L96 AND L68-L96

     FILE 'WPIX' ENTERED AT 07:56:45 ON 03 MAY 2005

=> d all abeq tech abex tot

L97  ANSWER 1 OF 9  WPIX  COPYRIGHT 2005 THE THOMSON CORP on STN
AN   2004-410146 [38]   WPIX
DNC  C2004-153912
TI   Stable intermediate for covalent conjugation with biologically active
     material to form conjugate for pharmaceutical composition comprises
     hyaluronan and other hydrophilic polymer(s) with functional group
     that reacts with divinyl sulfone.
DC   A96 B04
IN   LARSEN, N E; PARENT, E G
PA   (GENZ) GENZYME CORP
CYC  1
PI   US 2004087488   A1 20040506 (200438)*       6    A61K038-17
ADT  US 2004087488 A1 Provisional US 2002-393220P 20020702, US 2003-611439
     20030701
PRAI US 2002-393220P      20020702; US 2003-611439       20030701
IC   ICM  A61K038-17
     ICS  A61K031-716; A61K031-737; C08B037-00; C08B037-10
AB   US2004087488 A UPAB: 20040616
     NOVELTY - Stable intermediate for covalent conjugation with a biologically
     active material comprises a mixture of hyaluronan with at least
     one other hydrophilic polymer having a functional group capable of
     reacting with divinyl sulfone.
          DETAILED DESCRIPTION - Stable intermediate for covalent conjugation
     with a biologically active material comprises a mixture of
```

hyaluronan with at least one other hydrophilic polymer having a functional group capable of reacting with **divinyl sulfone.**

Stable intermediate for covalent conjugation with a biologically active material is of formula, P-O-CH2-CH2-SO2-(CH=CH2)n.

n = at least 1;

P = hydrophilic biopolymer having a functional group capable of reacting with **divinyl sulfone.**

INDEPENDENT CLAIMS are also included for:

(1) a conjugate comprising the reaction product of the intermediate and a biologically active material capable of being covalently and nucleophilically bonded to the intermediate;

(2) a method of preparing the intermediate, which comprises subjecting the hydrophilic biopolymer having a concentration of 0.01-1% at 4 deg. C to treatment with **divinyl sulfone** in the presence of a carbonate buffer at a pH of 9.6 for 30 minutes, and reducing the pH to 6.5 with hydrochloric acid to stop the reaction and leave free unreacted vinyl groups covalently attached to the hydrophilic biopolymer through -OH groups on it;

(3) a method of preparing the conjugate, which comprises reacting the intermediate with the biologically active material in aqueous solution at a pH of at least 9 at 4 deg. C in the presence of a carbonate buffer and shaken for 24 hours, and dialyzing the reaction mixture with saline solution to remove unreacted biologically active material;

(4) a pharmaceutical composition comprising the conjugate in a carrier or vehicle; and

(5) a method of treating an animal afflicted with a neoplastic condition, which comprises administering the pharmaceutical composition to the animal.

USE - The stable intermediate is used for covalent conjugation with a biologically active material to form a conjugate for use in a pharmaceutical composition (claimed).

ADVANTAGE - The conjugate not only retains the biological activity of the substance, but also exhibits enhanced, improved, and/or longer lasting activity than does the un-conjugated substance.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: A12-V01; B02-G; B04-C02A2; B04-C02D; B04-C02E; **B04-H05A;** B04-H19; B04-N02; B04-N06; B06-A03; B06-D18; B14-H01B

TECH UPTX: 20040616

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The biopolymer is a **hyaluronan** moiety or a moiety of a mixture of a **hyaluronan** with at least one other hydrophilic polymer. The **hyaluronan** is a hylan. The hydrophilic biopolymer is a natural or synthetic polysaccharide including hydroxyethyl cellulose, carboxymethyl cellulose, xanthan gum, chondroitin sulfate, or heparin; a protein including collagen, elastin, albumin, a globulin, keratin sulfate, a sulfated aminoglycosaminoglycan, or a synthetic water soluble polymer. The conjugate is of formula, HA-O-CH2-CH2-SO2-CH2-CH2-NH-INF. The intermediate is of formula, RO-CH2-CH2-SO2-CH2-CH2-O-(-CH2-CH2-SO2-CH2-CH2-O-)n-CH2-CH2-SO2-CH-. The biologically active material is R'OH, and the conjugate is of formula RO-CH2-CH2-SO2-CH2-CH2-O-(-CH2-CH2-SO2-CH2-CH2-O-)n-CH2-CH2-SO2-CH2-CH 2-OR.

HA = **hyaluronan** moiety or a moiety of a mixture of a **hyaluronan** with at least one other hydrophilic polymer;

INF = alpha-**interferon** moiety;

R = carbohydrate;

N = at least 0 and having a functional group capable of reacting with **divinyl sulfone;**

R' = a drug molecule, water, a protein, or an additional carbohydrate.

Preferred Property: The **hyaluronan** has a molecular weight of 1x103 to 1x107 Da.

Preferred Concentration: The concentration is 0.2-1%. The concentration of the hydrophilic biopolymer in the aqueous solution is 0.5%.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Substances: The biologically active substance is any substance having at least one chemical group reactive toward **divinyl sulfone** (DVS).
It is an antineoplastic, an antibiotic, a protein, an enzyme, or a peptide. The antineoplastic is vinblastin or paclitaxel, the antibiotic is gentamicin, the protein is alpha-**interferon** or cytochrome C, the enzyme is thrombin, and the peptide is avidin.

ABEX UPTX: 20040616
EXAMPLE - 0.05 g **hyaluronan** was dissolved in 10 ml sterile water. The final concentration was 5 mg per ml. After 2 days of mixing, the sample was autoclaved for 30 minutes at 121degreesC to reduce the molecular weight of the sample. The sample was subsequently diluted with 10 ml of 0.5 M carbonate buffer at pH 9.6, after which 5 microg of **vinyl sulfone** were added to the solution followed by vigorous mixing. The sample was placed on a shaker at 4degreesC for 30 minutes. The pH was adjusted to 6.5 by the addition of hydrochloric acid. The sample was placed in dialysis against 2 L of 0.1 M phosphate buffer pH 6.5 followed by dialysis against 800 volumes of water.

L97 ANSWER 2 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-441140 [41] WPIX
CR 2004-059227 [06]
DNC C2003-116646
TI New thioester terminated reactive polymer used for conjugating peptides, comprises water soluble and non peptidic polymer backbone with one of its terminus bonded to ethylenically unsaturated double bond containing structure.
DC A28 A96 B04
IN FANG, Z; ROBERTS, M J
PA (NEKT-N) NEKTAR THERAPEUTICS AL CORP; (SHEA-N) SHEARWATER CORP
CYC 101
PI WO 2003031581 A2 20030417 (200341)* EN 39 C12N000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003105224 A1 20030605 (200344) C08B037-00 <--
EP 1434589 A2 20040707 (200444) EN A61K031-74
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002360257 A1 20030422 (200461) C12N000-00
JP 2005505662 W 20050224 (200516) 71 C08G065-334
ADT WO 2003031581 A2 WO 2002-US32219 20021009; US 2003105224 A1 US 2001-973318 20011009; EP 1434589 A2 EP 2002-795502 20021009, WO 2002-US32219 20021009; AU 2002360257 A1 AU 2002-360257 20021009; JP 2005505662 W WO 2002-US32219 20021009, JP 2003-534552 20021009
FDT EP 1434589 A2 Based on WO 2003031581; AU 2002360257 A1 Based on WO 2003031581; JP 2005505662 W Based on WO 2003031581
PRAI US 2001-973318 20011009
IC ICM A61K031-74; **C08B037-00**; C08G065-334; C12N000-00
ICS C07K001-113; C07K014-555; C08G059-40
AB WO2003031581 A UPAB: 20050308
NOVELTY - Thioester-terminated reactive polymer (I) comprising a water soluble and non peptidic polymer backbone having at least one terminus bonded to an ethylenically unsaturated double bond containing structure (S1), is new.
DETAILED DESCRIPTION - Thioester-terminated reactive polymer (I)

comprising a water soluble and non peptidic polymer backbone having at least one terminus bonded to an ethylenically unsaturated double bond containing structure of formula L-(Z)a-CH(X))m-C(=Y)-Q (S1), is new.

L = point of bonding to the polymer backbone;
Z = a linker;
m = 0-12;
Y = a heteroatom;
X = H or alkyl;
a = 0 or 1, and
Q = S containing leaving group.

INDEPENDENT CLAIMS are also included for:

(1) a polymer conjugate (II) of a polypeptide having a cysteine or histidine residue at the N-terminus, where the polymer conjugate comprises a water soluble and non-peptidic polymer backbone having at least one terminus bonded to the structure of formula L-(Z)a-CH(X))m-C(=Y)-NH-CH(W)-polypeptide (S2);

(2) conjugating a polymer derivative to a polypeptide having a cysteine or histidine residue at the N-terminus, which comprises reacting a thioester terminated polymer comprising a water soluble and non peptidic polymer backbone having at least one terminus bonded to (S1) with a polypeptide having a cysteine or histidine residue at the N-terminus to form a conjugate of formula (S2), and

(3) a polymer conjugate (III) of a polypeptide having a cysteine molecule at the N-terminus, where the polymer conjugate comprises two water soluble and non-peptidic polymer backbones attached to the N-terminus, and the conjugate has a structure of formula (S4).

W = CH2SH or 1H-imidazolyl-4-methyl, and
L' = a linker.

USE - Used for site-specific polyethylene glycol attachment of polypeptides containing more than one free cysteine or histidine, even in the unfolded state. The polymers and the conjugation methods are useful for assisting insoluble polypeptides that are in the unfolded state to refold to their native conformation.

ADVANTAGE - Multiple protection and deprotection steps to prevent reaction of the polymer with other reactive groups and positions contained within the polypeptide are unnecessary. Site selective modification eliminates the need for additional conjugate purification steps to isolate particular (e.g. monopegylated) conjugate species. The use of thioester polymers provides water soluble polymer attachment, such as increased water solubility, increased plasma half-life, and decrease in proteolytic degradation as compared to an unmodified polypeptide.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: A10-E; A10-E24; A12-L04; A12-V01; A12-W11L; B04-C03; B04-G01; **B04-H05**; B04-H06; B04-J01; B04-K01; B04-L01; B04-N04
TECH UPTX: 20030630

TECHNOLOGY FOCUS - POLYMERS - Preferred Compounds: The polymer backbone comprises poly(alkylene glycol), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(alpha-hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N- acryloylmorpholine), polyacrylate, polyacrylamides, polysaccharides, their copolymers and/or terpolymers. The polymer backbone comprises poly(ethylene glycol) having a number average molecular weight of 100-100000 Da.

(I) Comprises R-poly-(Z)a-CH(X))m-CO-SR1 or R'-(poly-(Z)a-(CH(X))m-CO-S-R1)y.

poly = a water soluble and non-peptide polymer backbone, preferably polyethylene glycol;
R = a capping group or a functional group, preferably alkoxy, alkyl, benzyl, aryl, aryloxy, hydroxyl, active ester, active carbonate, acetal, aldehyde, aldehyde hydrate, alkenyl, acrylate, methacrylate, acrylamide, active sulfone, amine, hydrazine, thiol, carboxylic acid, isocyanate, isothiocyanate, maleimide, **vinylsulfone**, dithiopyridine,

vinylpyridine, iodoacetamide, epoxide, dione, glyoxal, mesylate, tosylate, tresylate or (Z)a-(CXH)m-CO-S-R1;
R' = a central core molecule, preferably a residue of polyols, polyamines or molecules having a combination of alcohol and amine groups, especially a residue of glycerol, glycerol oligomers, pentaerythritol, sorbitol or lysine, and
y = 3-100, and
R1 = H, or alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl (all optionally substituted), preferably phenol, nitrophenol, benzoic acid, pyridine, pyridinecarboxylic acid or nitropyridine.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Conjugate: The polypeptide comprises proteins, protein-ligands, enzymes, cytokines, hematopoietins, growth factors, hormones, antigens, antibodies, antibody fragments, receptors or protein fragments. Preferably, the polypeptide is an **interferon** molecule.

ABEX UPTX: 20030630

EXAMPLE - Preparation of 2-mercaptopyridine (40.0 mg), 1-hydroxybenzotriazole (4.0 mg), 4-(dimethylamino)pyridine (36.7 mg) and 1,3-dicyclohexylcarbodiimide (dissolved in 2 ml anhydrous dichloromethane, 84.0 mg) were added to a solution of PEG(5000)- alpha-methoxy-omega-propionic acid (1.5 g) in anhydrous acetonitrile (20 ml). The reaction solution was stirred overnight at ambient temperature under argon. The solution was then concentrated to near dryness at reduced pressure, followed by addition of anhydrous toluene (50 ml). The mixture was stirred at room temperature for 30 minutes, filtered and the filtrate was concentrated at reduced pressure to near dryness. Ethyl acetate (200 ml) was added and the mixture was warmed until the contents were completely dissolved. The solution was then cooled to room temperature while stirring. Ethyl ether (50 ml) was added and a precipitate formed. The product was filtered and rinsed with ethylether until the product became white. The product was then dried under high vacuum to give polyethylene glycol (PEG)(5000)-alpha- methoxy-omega-propionic acid, 2-pyridylthioester (PEG-PA-OPTE) (1.1 g).

Interferon tau (0.45 mg) was formulated to 0.3 mg/ml in 0.33 M Tris, 0.7 mM TCEP (Tris(2-carboxyethylphosphine) hydrochloride) at pH 7.75. 1.0 mg of mPEG5k-PA-OPTE (orthopyridyl thioester of the above propionic acid) was added to the **interferon** solution and reacted at room temperature for 4 hours. The product was analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE). The gel showed two bands corresponding to unconjugated **interferon** (20 kDa) and singly PEG-conjugated **interferon** (29 kDa) (i.e., a polypeptide attached to a single PEG molecule). The slower migration of PEG-**interferon** conjugate was due to the larger hydrodynamics volume of the PEG chain when compared to a corresponding molecular weight protein.

L97 ANSWER 3 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-210016 [20] WPIX
CR 2003-120441 [11]
DNC C2003-053404
TI Novel conjugate molecule, for selectively delivering diagnostic agent to apoptotic cells, comprises ligand bonded to polymer, chelating agent bonded to polymer, and radioisotope chelated to chelating agent.
DC A96 B04 D16 K08
IN ELLIS, L M; LI, C; WALLACE, S; WEN, X; WU, Q
PA (ELLI-I) ELLIS L M; (LICC-I) LI C; (WALL-I) WALLACE S; (WENX-I) WEN X; (WUQQ-I) WU Q; (TEXA) UNIV TEXAS SYSTEM
CYC 101
PI WO 2002087498 A2 20021107 (200320)* EN 84 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2003003048 A1 20030102 (200320) A61K051-00
EP 1389090 A2 20040218 (200413) EN A61K009-127
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
AU 2002307444 A1 20021111 (200433) A61K000-00

ADT WO 2002087498 A2 WO 2002-US12510 20020419; US 2003003048 A1 Provisional US 2001-286453P 20010426, Provisional US 2001-334969P 20011204, Provisional US 2001-343147P 20011220, US 2002-126216 20020419; EP 1389090 A2 EP 2002-766783 20020419, WO 2002-US12510 20020419; AU 2002307444 A1 AU 2002-307444 20020419

FDT EP 1389090 A2 Based on WO 2002087498; AU 2002307444 A1 Based on WO 2002087498

PRAI US 2001-343147P 20011220; US 2001-286453P 20010426;
US 2001-334969P 20011204; US 2002-126216 20020419

IC ICM A61K000-00; A61K009-127; A61K051-00
ICS C07H001-00; C07K014-00; C07K016-46; C08H001-00; C12N009-00

AB WO 200287498 A UPAB: 20040525

NOVELTY - A conjugate molecule (I) comprising a ligand bonded to a polymer, a chelating agent (CA) bonded to the polymer, and a radioisotope chelated to the chelating agent, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I) and a carrier; and

(2) synthesizing (I).

ACTIVITY - Cytostatic; Immunosuppressive; Antiinflammatory; Vasotropic; Antisickling; Antianemic; Neuroprotective; Antirheumatic; Antiarthritic.

MECHANISM OF ACTION - Inducer of apoptosis; Inhibitor of tumor cell growth.

DiFi cells were seeded at 5 multiply 104 cells/well onto 24-well culture plates. Cell viability after 72 hour treatment of the cells with C225 or diethylenetriamine-pentaacetic acid (DTPA)-polyethylene glycol (PEG)-C225 was assayed by adding 50 micro l of 10 mg/ml 3,-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into 0.5 ml of culture medium and incubating the cells for 3 hours at 37 deg. C in a CO2 incubator, followed by cell lysis with 500 micro l of lysis buffer containing 20 % sodium dodecyl sulfate (SDS) in dimethyl formamide/H2O, pH 4.7, at 37 deg. C for more than 6 hours. An optical absorbance of cell lysate was determined by measuring the cell lysate at a wavelength of 595 nm and normalizing the value with the corresponding control of untreated cells. Blocking of epidermal growth factor receptor (EGFR) tyrosine kinase activity with C225 leads to cell cycle arrest and subsequent cell death through apoptosis in DiFi cells. While the linker molecule PEG-DTPA itself had no effect on DiFi cell growth, all three conjugates, 1:10, 1:20 and 1:40 DTPA-PEG-C225, inhibited the tumor cell growth to the same extent as native C225, indicating that all conjugates were capable of inducing apoptosis in the DiFi human colon cancer cells.

USE - (I) is useful for selectively delivering a diagnostic agent to apoptotic cells in a patient, by administering (I) to the patient having apoptotic cells, where (I) comprises a ligand bonded to a polymer, where the ligand is annexin V, CA bonded to the polymer, and a radioisotope chelated to CA. The patient is a mammal, preferably human. The apoptotic cells are present following treatment of a target tissue which is a tumor. (I) is useful for treating a patient suspected of having a tumor, by administering (I) to the patient, where the ligand has affinity for the tumor, and for visualizing tumors or apoptotic cells. The radioisotope is 90Y, 64Cu, 111In or 67Cu. The ligand is antibody or protein, preferably, Herceptin, C225 or annexin V. The polymer is polyethylene glycol and CA is diethylenetriamine-pentaacetic acid (DTPA) or tetraazacyclododecane-N,N',N,N'-tetraacetic acid (DOTA). The tumor is a solid tumor, breast

cancer tumor, ovarian cancer tumor, colon cancer tumor, lung cancer tumor, head and neck cancer tumor, brain tumor, liver cancer tumor, pancreatic tumor, bone cancer tumor or prostate cancer tumor. The detection step of the radioisotope is by radioscintigraphy, single photon emission computed tomography or positron emission tomography. The apoptotic cells are associated with a disease or condition such as acute organ transplant rejection, inflammatory disease, infectious disease, regenerative tissue, post-surgery tissue, post-trauma tissue, hypoxic ischemic cerebral reperfusion injury, toxic effect of a chemotherapeutic agent to normal tissue, sickle cell disease, thalassemia, multiple sclerosis and rheumatoid arthritis. (I) is also useful for visualizing tumors or apoptotic cells, by administering (I) to a patient suspected of having a tumor or apoptotic cells, and detecting (I), where (I) comprises a ligand bonded to a polymer and a near-infrared dye bonded to the polymer, and where the ligand has affinity for the tumor or apoptotic cells. The near-infrared dye is indocyanine green (ICG) or an ICG derivative. The near-infrared dye is detected by near-infrared camera. (I) is also optionally combined with a diagnostic agent. (All claimed.) (I) or (II) is useful for monitoring treatment of tumors and other tissues with biological receptors, and in diagnostic, therapeutic, research and other applications.

ADVANTAGE - (I) is synthesized without the necessity of preactivation of the ligand using an SCN-polymer-chelating agent precursor.

DESCRIPTION OF DRAWING(S) - The drawing shows the synthesis of polyethylene glycol (PEG)-modified antibodies.

Dwg.1/21

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; A12-V01; A12-V03C2; B04-C02; B04-C03; B04-G01; B04-G21; B04-G2100E; **B04-H05**; B04-H06; B04-H08; B04-N04; B04-N06; B05-A03B; B05-A04; B05-B01A; B05-B01G; B06-D13; B07-D13; B10-A22; B10-B01B; B10-C02; B14-A01; B14-C03; B14-C09B; B14-F02D; B14-F03; B14-G02C; B14-H01; B14-S01; D05-H09; D05-H10; D05-H12E; K08-X; K09-B; K09-E

TECH UPTX: 20030324

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Preparation: (I) is synthesized by:

(a) providing a polymer conjugate (PC)-SCN precursor, where the SCN group is covalently bonded to PC, and combining a ligand with PC-SCN precursor to form a ligand-PC molecule, where the ligand is covalently bonded to the polymer;

(b) providing PC comprising at least one thio (SH) group covalently conjugated to PC, providing a ligand comprising at least one thio reactive group, and combining PC and the ligand to form a ligand-PC molecule; and

(c) providing PC and a ligand, where one of the PC or ligand comprises a thio group, and the other of the PC or the ligand comprises a thio reactive group, and combining PC and the ligand to form a ligand-PC molecule, where the ligand is covalently bonded to the polymer by a thioether (S-C) bond.

The ligand comprises a primary amino group. The method further involves combining the ligand-PC molecule with a diagnostic agent to form a ligand-polymer-CA-diagnostic agent conjugate molecule. The diagnostic agent is a radioisotope. PC comprises a polymer covalently bonded to a therapeutic agent such as a diagnostic agent e.g. a dye molecule, or CA. PC-SCN precursor comprises a polymer chosen from polyethylene glycol, poly(l-glutamic acid), dextran, polyvinyl alcohol, polyethylene oxide-polypropylene oxide copolymer and copolymers between two or more of it. The ligand is pretreated with an agent to introduce at least one thio-reactive group. The agent is **vinyl sulfone** or maleimide. Providing PC involves obtaining a precursor PC having a protected thio group, and treating the precursor polymer with a deblocking agent to release a free thio group. The thio group is attached to the ligand and the thio reactive group is attached to PC, and PC is prepared

by attaching SPDP or maleimide to PC, or the thio group is attached to PC and the thioreactive group is attached to the ligand and the ligand is pretreated with maleimide or **vinyl sulfone** to introduce the thio reactive group. (All claimed.)
Preferred Conjugate Molecule: The ligand is covalently bonded to the polymer and CA is covalently bonded to the polymer. The ligand is a peptide, protein, antibody or antibody fragment. The ligand is chosen from 34 ligands given in the specification such as C225, Herceptin, Rituxan, annexin V, C225 or antibody. The polymer is polyethylene glycol which has an average molecular weight of 1000 Da to 100000 Da, a polysaccharide or polyamino acid having an average molecular weight of 1000 Da to 150000 Da, poly(l-glutamic acid), poly(d-glutamic acid), poly(dl-glutamic acid), poly(l-aspartic acid), poly(d-aspartic acid), poly(dl-aspartic acid), polylysine, polysaccharide, dextran, polypropylene oxide (PPO), polyvinyl pyrolidone, polyvinyl alcohol, polyethylene glycol, **hyaluronic acid**, chitosan, dextran, polyacrylic acid, poly(2-hydroxyethyl 1-glutamine) or carboxymethyl dextran. The polymer is a copolymer between two or more of the above polymers. CA is chosen from any one of the 38 agent given in the specification e.g. diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine (EC) or dimercaptosuccinic acid (DMSA) The radioisotope is 111In, 67Ga, 68Ga, 82Rb, 86Y, 90Y, 99mTc, 64Cu, 67Cu, 193Pt, 113mIn or 201Tl, preferably 111In.

ABEX UPTX: 20030324
WIDER DISCLOSURE - A kit comprising (I) or (II), is also disclosed.

ADMINISTRATION - (I) is administered through intravascular, intraperitoneal, intramuscular or intratumoral injection (claimed). No dosage is given.
EXAMPLE - Diethylenetriamine-pentaacetic acid (DTPA)-polyethylene glycol (PEG)-C225 (anti-epidermal growth factor receptor (EGFR) antibody) was synthesized as follows. To a stirred suspension of DTPA-dianhydride (143 mg, 0.4 mmoles) in 4 ml chloroform was added triethylamine (TEA) (81 mg, 0.8 mmoles) and t-butoxycarbonyl(Boc)-NH-PEG-NH2 (340 mg, 0.1 mmol). The mixture was allowed to react at room temperature for 2 hours. NH2-PEG-NH-t-Boc was converted to DTPA-PEG-NH-t-Boc. After the reaction, the chloroform and TEA were removed under vacuum. The t-Boc protecting group was also removed. The resulting DTPA-PEG-NH2 was purified. DTPA-PEG-NH2 (182 mg, 0.05 mmol) was reacted with N-succinimidyl s-acetylthioacetate (SATA) (14 mg, 0.06 mmol) in chloroform at room temperature for 1 hour, and then purified to afford DTPA-PEG-ATA. To an aqueous solution of C225 (2.4 mg/ml; 4.8 mg, 0.032 pmol) at room temperature was added aliquots of N-gamma-maleimidobutyryloxysuccinimide ester (GMBS) in dimethylformamide (DW) (2.8 mg/ml). The mixture was stirred, and purified by gel filtration. Prior to conjugation with activated C225, the acetyl protecting group in DTPA-PEG-ATA was removed using hydroxylamine. For this purpose, an aliquot of NH2OH in 0.1 M Na2HPO4 was added to a solution of DTPA-PEG-ATA in 0.1 M Na2HP)4, then incubated at room temperature for 30 minutes. The resulting DTPA-PEG-SH containing free sulfhydryl group was then mixed with maleimide-activated C225 with DTPA-PEG-SH-to-maleimide molar ratio of 2:1 and incubated at 4degreesC overnight. The final product was separated from unreacted DTPA-PEG. Four DTPA-PEG-C225 conjugates with different degrees of C225 modification were synthesized. These conjugates were designated as 1:10, 1:20, 1:30 and 1:40 DTPA-PEG-C225, with the numbers being the molar ratios of antibody to GMBS in the maleimide-activating reaction.

L97 ANSWER 4 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-120441 [11] WPIX
CR 2003-210016 [20]
DNC C2003-031027
TI New conjugate molecules useful for the selective delivery of therapeutic agents to tumors or other tissues expressing biological receptors.
DC A96 B05 B07

IN KE, S; LI, C; VEGA, J O; WALLACE, S
PA (KESS-I) KE S; (LICC-I) LI C; (VEGA-I) VEGA J O; (WALL-I) WALLACE S; (TEXA) UNIV TEXAS SYSTEM
CYC 100
PI WO 2002087497 A2 20021107 (200311)* EN 46 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2002197261 A1 20021226 (200311) A61K039-395
AU 2002258895 A1 20021111 (200433) A61K000-00
ADT WO 2002087497 A2 WO 2002-US12502 20020419; US 2002197261 A1 Provisional US 2001-286453P 20010426, Provisional US 2001-334969P 20011204, Provisional US 2001-343147P 20011220, US 2002-126369 20020419; AU 2002258895 A1 AU 2002-258895 20020419
FDT AU 2002258895 A1 Based on WO 2002087497
PRAI US 2001-343147P 20011220; US 2001-286453P 20010426;
US 2001-334969P 20011204; US 2002-126369 20020419
IC ICM A61K000-00; A61K039-395
ICS C07K016-46
AB WO 200287497 A UPAB: 20040525
NOVELTY - A new conjugate molecule comprising:
(1) a ligand (a);
(2) a polymer spacer (b);
(3) a polymer carrier (c); and
(4) and a therapeutic agent (d)
Where (a) is bonded to (b), (b) is bonded to (c) and (c) is bonded to (d).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) A composition (A1) comprising a nanoparticle, which comprises several conjugate molecules;
(2) Selectively delivering (d) to a target tissue in a patient involving administering the conjugate molecule to the patient where (a) is with affinity for the target tissue; and
(3) Preparation of the conjugate molecule.
ACTIVITY - Cytostatic; Antitumor; Anti-inflammatory; Virucide.
MECHANISM OF ACTION - Tumor growth inhibitor.
USE - For selectively delivering a therapeutic agent to a target tissue (e.g. tumor, (preferably solid tumor selected from breast cancer, ovarian cancer, colon cancer, lung cancer, head and neck cancer, brain cancer, liver cancer, pancreatic cancer, bone cancer, prostate cancer, lymphoma or leukemia), an inflammatory tissue, infectious tissue, a reparative tissue and regenerative tissue) and for treating a patient having a diseased tissue (e.g. the tumor, the inflammatory tissue, infections tissue, the reparative tissue and regenerative tissue) in a patient (e.g. mammal or human) (claimed).
ADVANTAGE - The conjugate provide enhanced cellular uptake of the polymeric construct into tumor cells overexpressing EGF receptors and for Her2/neu receptors and maintain the binding affinity of the corresponding monoclonal antibodies. The conjugate has improved in vivo half lives and exhibit reduced or eliminated accumulation in the liver. The use of polymers reduces non-specific interaction with non-target tissues and reduces background activity. Attachment of the therapeutic agent and polymer carrier to the ligand with a polymer spacer instead of to the ligand directly improves retention of the ligand's receptor binding affinity. The conjugate molecule design strategy is flexible and allows for the preparation of a wide array of molecules for different diagnostic and clinical uses and allows both targeting passive and active targeting.
Dwg.0/13
FS CPI

FA AB; DCN
MC CPI: A12-V01; B04-C01; B04-C02C; B04-C02D; B04-C02E; B04-C03B; B04-C03D; B04-G01; B05-A03B; B06-A02; B06-A03; B06-E05; B10-A07; B11-C07A5; B14-A01; B14-C03; B14-H01; B14-S12
TECH UPTX: 20030214

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Molecule: The bonding in the conjugate molecule between constituents is cola.

Preparation (claimed): Preparation of the conjugate molecule involves:

(a) Process (A):

(i) (a1) providing a polymer spacer-polymer carrier construct having a sulfhydryl-reactive **vinyl sulfone** group at the end of (b);

(ii) (b1) conjugating (d) to (c) to form a **vinyl sulfone** -polymer spacer-polymer carrier-therapeutic agent construct;

(iii) (c1) pretreating (a) to introduce sulfhydryl groups on (a) and (d1) combining the pretreated ligand with the **vinyl sulfone** -polymer spacer-polymer carrier-therapeutic agent construct and reacting the **vinyl sulfone** group with the sulfhydryl group;

(b) Process (B):

(i) (a2) introducing a protected sulfhydryl group (SH) to an end of (b);

(ii) (b2) conjugating (b) to (c) to form protected SH-polymer spacer-polymer carrier construct;

(iii) (c2) conjugating (d) to (c) to form a protected SH-polymer spacer-polymer carrier-therapeutic agent construct;

(iv) (d2) pretreating (a) to introduce a SH reactive functional group on (a);

(v) (e2) deprotecting the protected SH group to obtain a free SH group, and combining the pretreated ligand with the construct such that the SH group reacts with the SH reactive functional group to form the conjugate molecule;

(c) Process (c):

(i) (a3) providing a polymer spacer-polymer carrier-therapeutic agent construct;

(ii) (b3) introducing a protected amine to an end of the (b) to form a protected amine-polymer spacer-polymer carrier-therapeutic agent construct;

(iii) (c3) deprotecting the construct obtained in the step (b3) to obtain a free amine-polymer spacer-polymer carrier-therapeutic agent construct; and

(iv) (d3) combining the construct obtained in the step (c3) with a ligand having a carboxylic acid group which conjugates with the free amine to form an amide bond, thus forming the conjugate molecule.

The step (d2) is carried out by pretreating (a) with **vinyl sulfone** or maleimide to introduce the SH reactive functional group.

Preferred Components: (d) is chemotherapeutic agent (preferably Adriamycin, daunorubicin, paclitaxel (Taxol), docetaxel (taxotere), epothilone, camptothecin, cisplatin, carboplatin, etoposide, tenoposide, geldanamycin, methotrexate and maytansinoid DM1, 5-FU or gadolinium-DTPA (especially Adriamycin or paclitaxel)).

(c) is bonded to (d) with a linker.

(a) is an antibody, an antibody fragment, a peptide or protein (preferably C225, Herceptin, Rituxan, a phage library antibody, anti-CD, DC101, an antibody to integrin alpha v-beta 3, LM609, an antibody to VEGF, an antibody to VEGF receptor, F(ab')2, Fab', ScFv fragment, C7E3Fab, a growth factor, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PDGF, Angiopoietin-1, Angiopoietin-2-, HGF, EGF, bFGF, cyclic CTTHWGFTLC, cyclic CNGRC, cyclic RGD-4C, annexin V, an **interferon**, a tumor necrosis factor, endostatin, angiostatin or thrombospondin, especially the antibody (preferably the monoclonal antibody), C225, Herceptin, c7E3Fab or annexin V).

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (b) is polyethylene

glycol, polyamino acid, polytyrosine, polyphenylalanine, dextran, polysaccharide, polypropylene oxide, copolymer of polyethylene glycol with polypropylene oxide, polyglycolic acid, polyvinyl pyrrolidone, polylactic acid or polyvinyl alcohol (preferably polyethylene glycol having a number average molecular weight of 1000 - 100000 daltons).
(c) is poly(l-glutamic acid), poly(d-glutamic acid), poly(dl-glutamic acid), poly(l-aspartic acid), poly(d-aspartic acid), poly(dl-aspartic acid), polylysine, polysaccharide, polyhydroxypropylmethacrylamide, dextran, poly(hydroxypropylglutamine), poly(hydroethylglutamine), **hyaluronic acid**, carboxymethyl dextran, polyacrylic acid or chitosan or their copolymers (preferably poly(l-glutamic acid having a number average molecular weight of 1000 - 100000 daltons).

ABEX UPTX: 20030214

ADMINISTRATION - The administration of the conjugate molecule is intravascular, intraperitoneal or intramuscular injection (claimed). The route of administration can be by another parenteral route e.g. by intratumor. No dosage given.
EXAMPLE - poly-glutamic acid (PG) (500 mg) in 1M phosphate buffer was added to sulfonyl reactive **vinyl sulfone** (VS)-PEG-NHS in five fractions for 2 hours. The mixture was stirred for 5 hours at room temperature. The reaction was stopped by acidifying the mixture with 1N HCl to pH 3 and the precipitate was recovered, followed by washing two times with distilled water and lyophilizing to obtain the conjugate product of VS-PEG-PG (A) in acid form.
Into a solution of (A) (250 mg) in dimethyl formamide (DMF) (10 ml) was dissolved paclitaxel (150 mg), diisopropylcarbodiimide (DIC) (30 mg), pyridine (75 micro l) and a trace amount of dimethylamino pyridine (DMAP). The reaction mixture was stirred overnight at room temperature, followed by evaporation of the solvent. The residue obtained was dissolved in 0.1N NaHCO3. The aqueous solution was filtered and dialyzed to obtain VS-PEG-PG-TXL (A1). The fluorescent dye BODIPY was conjugated to (A) to facilitate confocal fluorescent microscopic study. Into a solution of Herceptin (50 mg) was added an aliquot of S-acetyl thioacetate (SATA) in DMF (190 micro l). After stirring for 1 hour at room temperature, hydroxylamine aqueous solution (0.5 ml) was added into the solution. The mixture was stirred for 2 hours, concentrated to 1 - 2 ml by ultracentrifugation. The resulting SH-containing mAb was purified. mAb was mixed with (A1) with a molar ratio of mAb to polymer of 1:8 - 1:10. After stirring at 4 degrees C, the sodium was passed through a nickel affinity column to remove unreacted polymer, followed by purification to remove free mAb from polymer bound mAb. The yield of mAb was 8 - 10%. The molar ratios of Herceptin to PEG - PG polymer was based on the measurements of protein and BODIPY FL concentrations. The molar ratio of Herceptin to PEG - PG was 1:8, followed by a purification step to obtain a conjugate of Herceptin-PEG-PG-TXL molecule (A2).

L97 ANSWER 5 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2002-240928 [29] WPIX
DNC C2002-072381
TI New drug delivery system for treating diabetes comprises macromolecular drug complex containing a drug and a polymer having several acid groups.
DC A96 B05 B07
IN DADEY, E J; ZAMIRI, C
PA (UNII) UNIV ILLINOIS; (UNII) UNIV ILLINOIS FOUND
CYC 97
PI WO 2001093911 A2 20011213 (200229)* EN 61 A61K047-30
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001063277 A 20011217 (200229) A61K047-30

US 6417237 B1 20020709 (200253) A61K009-107
EP 1286659 A2 20030305 (200319) EN A61K009-107
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001011506 A 20030624 (200343) A61K047-30
CN 1441666 A 20030910 (200380) A61K009-107
JP 2003535149 W 20031125 (200380) 53 A61K045-00
ZA 2002009229 A 20031029 (200381) 77 A61K000-00

ADT WO 2001093911 A2 WO 2001-US16163 20010517; AU 2001063277 A AU 2001-63277 20010517; US 6417237 B1 US 2000-589721 20000608; EP 1286659 A2 EP 2001-937558 20010517, WO 2001-US16163 20010517; BR 2001011506 A BR 2001-11506 20010517, WO 2001-US16163 20010517; CN 1441666 A CN 2001-810825 20010517; JP 2003535149 W WO 2001-US16163 20010517, JP 2002-501482 20010517; ZA 2002009229 A ZA 2002-9229 20021113

FDT AU 2001063277 A Based on WO 2001093911; EP 1286659 A2 Based on WO 2001093911; BR 2001011506 A Based on WO 2001093911; JP 2003535149 W Based on WO 2001093911

PRAI US 2000-589721 20000608

IC ICM A61K000-00; A61K009-107; A61K045-00; A61K047-30
ICS A61K038-22; A61K038-27; A61K038-28; A61K047-32; A61K047-36; A61K047-46; A61K047-48; A61P003-06; A61P003-10; A61P005-06; A61P009-12; A61P015-00; A61P019-10; A61P021-00; A61P025-00; A61P025-24

AB WO 200193911 A UPAB: 20020508

NOVELTY - A drug delivery system comprises a macromolecular drug complex (a). (a) comprises a drug (b) having at least one quaternary ammonium nitrogen atom and a polymer (c) having several acid groups and a weight average molecular weight of 1000 - 50000. (a) has a weight ratio of (b) to (c) of 10:90 - 90:10 and is incorporated into a microemulsion.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a drug composition comprising (a) and a microemulsion comprising an oil, an amphiphile and water.

ACTIVITY - Antidiabetic; Antilipemic; Hypotensive; Antidepressant; Osteopathic; Vasotropic.

Male, New Zealand white rabbits (each approx. 3 - 4 kg), were fasted and each rabbit received one of the following growth hormone (GH) formulations: (1) 1.8 micro g/kg GH-haparin complex intravenously (IV); (2) 1.8 micro g/kg GH solution intravenously; (3) 36 micro g/kg GH-heparin complex solution, via intratracheal administration (IT), or (4) 36 micro g/kg GH-heparin complex microemulsion, via (IT) administration. Blood (approx. 0.50 ml) was collected periodically from the marginal ear vein, and glucose levels were determined using One Touch (glucometer). The results showed that serum glucose levels decreased following intravenous (IV) administration of a GH solution alone or a macromolecular GH-heparin complex formulated in a microemulsion, serum glucose level showed a similar hypoglycemic response following (IT) administration of the GH-heparin-macromolecular complex and following the administration of the GH-heparin microemulsion. The results showed that GH was absorbed following (IT) administration of GH-heparin complex or the GH-heparin microemulsion. In addition, the administration of the microemulsion containing the macromolecular GH-heparin complex had the advantage of lessening the acute hypoglycemic effect that was associated with GH-therapy. The results also showed a delayed hypoglycemic effect by the microemulsion and macromolecular drug complex compared to the GH solution.

MECHANISM OF ACTION - None given.

USE - For treating diabetes and vascular complications associated with diabetes by using insulin as the drug; for treating a disease or a condition e.g. dwarfism, hypopituitarism, hypercholesterolemia, hypertension, depression, muscle wasting, osteoporosis, insomnia, menopause, impotence, and a condition associated with aging, by using human growth hormone as the drug (all claimed).

ADVANTAGE - The system provides the administration of difficult to administer drug, like insulin and human growth hormone by easier way. The

system makes it possible to regulate the pharmacologic response. The macromolecular drug complexes can be water-soluble or water-insoluble at neutral pH and thus can be administered in a variety of dosage forms.
Dwg.1/12

FS CPI

FA AB; GI; DCN

MC CPI: A10-E; A10-E21; A12-V01; B02-Z; B04-C01; B04-C02; B04-C02D; B04-C02E1; B04-C02E2; B04-C03; B04-C03B; **B04-H05**; B04-J03A; B04-J03B; B04-J05J; B04-N04; B05-B01J; B06-H; B07-D04C; B07-D08; B10-A07; B10-B02A; B10-B02D; B12-M03; B14-D01; B14-D02A2; B14-E11; B14-F02B; B14-F06; B14-J01A1; B14-J01B2; B14-J01B4; B14-J05; B14-N01; B14-S02; B14-S04

TECH UPTX: 20020508

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drug: (b) is a polypeptide or a protein (preferably insulin, human growth hormone, tereofenamate, proglumetacin, tiaramide, apazone, benzpipierylon, pipebuzone, ramifenazone, methotrexate, isoniazid, polymyxin, bacitracin, tuber-actionomycin, ethryomycin, penicillamine, chloroquine phosphate, glucosamine, hydroxy-chloroquine, glucagon, cyclophosphamide, **interferon** alpha, **interferon** beta, **interferon** gamma, vincristine or vinblastine, especially insulin, human growth hormone, methotrexate, polymyxin, bacitracin, tuberactionomycin, chloroquine phosphate, glucagon, **interferon** alpha, **interferon** beta or **interferon** gamma, particularly insulin or human growth hormone).
Preferred System: The weight ratio of (b) to (c) is 10:90 - 75:25 (preferably 12.5:87.5 - 50:50). (c) is in a free acid or salt form. (a) is soluble but water insoluble at an acidic pH.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (c) comprises a monomer (25 - 100 wt.%) having an acid group selected from carboxyl, phosphate, phosphonate, sulfate, sulfonate and/or phenolic (preferably sulfated or sulfonated aromatic monomer). (c) has the weight average molecular weight (Mw) of 2000 - 20000 (preferably 4000 - 15000) and is lightly crosslinked. (c) is a naturally occurring polymer having Mw of 1000 - 12000 or a synthetic polymer. The naturally occurring polymer is heparin, dermatan sulfate, chondroitin sulfate, keratan sulfate, heparin sulfate, **hyaluronic acid** and/or carrageenan. The synthetic polymer is a homopolymer of an alpha,beta-unsaturated carboxylic acid or a copolymer of an alpha,beta-unsaturated carboxylic acid and a comonomer. (c) is polyacrylic acid, polyvinylphosphonic acid, **polyvinylsulfonic** acid, polystyrenesulfonic acid, polymaleic acid, polymethacrylic acid, polyvinylsulfuric acid, poly(2-methacroyloxymethane-1-sulfonic acid, poly(4-vinylbenzoic acid), poly(3-(vinyloxy)propane-1-sulfonic acid), poly(4-vinylphenol), poly(4-vinylphenyl sulfuric acid) and/or poly(N-vinyl-succinamidic acid) (preferably polyvinylphosphonic acid and polyacrylic acid).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The comonomer is ethylene, propylene, 4-5C alkene, 1-12C ester of an alpha,beta-unsaturated carboxylic acid ester, vinyl propionate, (meth)acrylamide, styrene, alpha-methyl toluene, vinyl toluene, vinyl pyrrolidone, vinyl alcohol, vinyl acetate and/or vinyl alkyl ether. The alpha,beta-unsaturated carboxylic acid is (meth)acrylic acid, maleic acid, fumaric acid, itaconic acid, mesaconic acid, citraconic acid and/or vinylphosphonic acid.
Preferred Composition: The microemulsion is a water-in-oil or an oil-in-water emulsion.

ABEX UPTX: 20020508

ADMINISTRATION - The microemulsion is administered intravenously or orally (claimed). The drug delivery system is also administered orally, parenterally, sublingually, transdermally, conjunctivally, intraocularly, intranasally, aurally, intrarespiratory, rectally, vaginally or

urethrally.

EXAMPLE - None given.

L97 ANSWER 6 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-607216 [69] WPIX
DNN N2001-453275 DNC C2001-180416
TI Preparing water-insoluble biocompatible compositions used to prevent post-surgical adhesions includes reacting polyanionic polysaccharide with **divinylsulfone** in aqueous solution to form gel.
DC A96 B07 D22 P34
IN CALIAS, P; MILLER, R J
PA (GENZ) **GENZYME CORP**
CYC 95
PI WO 2001060868 A1 20010823 (200169)* EN 20 C08B037-08 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001038108 A 20010827 (200176) C08B037-08 <--
EP 1263793 A1 20021211 (200301) EN C08B037-08 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6521223 B1 20030218 (200317) A61K031-74
JP 2003523237 W 20030805 (200353) 23 A61L031-00
ADT WO 2001060868 A1 WO 2001-US4267 20010209; AU 2001038108 A AU 2001-38108 20010209; EP 1263793 A1 EP 2001-910512 20010209, WO 2001-US4267 20010209; US 6521223 B1 US 2000-503544 20000214; JP 2003523237 W JP 2001-560250 20010209, WO 2001-US4267 20010209
FDT AU 2001038108 A Based on WO 2001060868; EP 1263793 A1 Based on WO 2001060868; JP 2003523237 W Based on WO 2001060868
PRAI US 2000-503544 20000214
IC ICM A61K031-74; A61L031-00; **C08B037-08**
ICS A61F002-00; A61F013-00; A61K009-00; A61K047-00; A61K047-36; A61L031-06; **C08B011-20**; **C08B015-00**; **C08B031-00**; **C08B037-00**; C08J003-075; C08J003-24
AB WO 200160868 A UPAB: 20011126
NOVELTY - Methods for preparing water-insoluble biocompatible compositions comprise:
(a) reacting a polyanionic polysaccharide with **divinylsulfone** in an aqueous solution to form a gel;
(b) neutralizing the pH of the solution; and
(c) precipitating a solid from the solution.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for
(1) a sterilized single phase gel product; and
(2) a method for the prevention of adhesions in a human patient comprising applying the gel to a region between two tissue surfaces to be separated during the healing process following surgery.
USE - The methods are used to prepare water-insoluble biocompatible compositions and single-phase gel products (claimed), which are used to prevent adhesions between two tissue surfaces to be separated during the healing process following surgery such as abdominal, pelvic, gynecological, orthopedic and cardiac surgery.
ADVANTAGE - The methods produce single-phase gel products that are easily handled and stored for future use, but possess the advantageous characteristics of two-phase gels.
Dwg.0/0
FS CPI GMPI
FA AB; DCN
MC CPI: A03-A00A; A10-E22; A12-V03A; B04-C02; B10-A10; B11-C04; D09-D
TECH UPTX: 20011126

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The polyanionic polysaccharide is **hyaluronic acid, sodium hyaluronate**, potassium **hyaluronate**, magnesium **hyaluronate**, calcium **hyaluronate**, carboxymethylcellulose (CMC), carboxymethylamylose or a mixture of **hyaluronic acid** and CMC. After (c), the solid precipitated from the solution is rehydrated to form a gel, which is preferably heated to 100-150degreesC. The molar ratio of **divinyl sulfone** to **hyaluronic acid** is 0.1:1-1:1 (0.2:1-0.6:1). The compositions further comprise a drug.

ABEX UPTX: 20011126

EXAMPLE - 0.2N Sodium hydroxide solution (200 ml) was added to **hyaluronic acid** (8 g) and the mixture was stirred at room temperature (RT) until full dissolution (approximately3 hours). **Divinyl sulfonate** (266 ml) was added and the solution was stirred vigorously for approximately1 minute. The reaction was allowed to stand at RT for 1 hour. The gel was placed in deionized water for 24 hours, chopped into four pieces and allowed to stand in phosphate-buffered saline (PBS) for 24 hours. PBS (5 ml) was added to the swollen gel and the mixture was mixed under high shear conditions. The pH was adjusted to 7.2 using 6N hydrochloric acid. Absolute ethanol (3 l) was added to bring about precipitation. The precipitate was collected and dried under vacuum. The powder was easily rehydrated upon addition of PBS and high shear mixing.

L97 ANSWER 7 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1989-174458 [24] WPIX
CR 1986-183142 [29]
DNC C1989-077145
TI Chemically modified **hyaluronic acid** - prepared by treating suitable animal tissue with aldehyde and extraction at alkaline pH and low temperature.
DC A96 B04 D21
IN BALAZS, E A; BAND, P; **LARSEN, N E**; LESHCHINER, A; LESHCINER, A
PA (BIOM-N) BIOMATRIX INC
CYC 13
PI EP 320164 A 19890614 (198924)* EN 17
R: BE CH DE FR GB IT LI NL SE
AU 8822263 A 19890615 (198932)
JP 01197502 A 19890809 (198938)
US 5099013 A 19920324 (199215) 25
CA 1327569 C 19940308 (199415) C08B037-08 <--
EP 320164 B1 19950208 (199510) EN 20 C08B037-08 <--
R: BE CH DE FR GB IT LI NL SE
DE 3852992 G 19950323 (199517) C08B037-08 <--
JP 2510264 B2 19960626 (199630) 21 C08B037-08 <--
ADT EP 320164 A EP 1988-311301 19881129; JP 01197502 A JP 1988-312775 19881210; US 5099013 A US 1990-616706 19901116; CA 1327569 C CA 1988-581683 19881028; EP 320164 B1 EP 1988-311301 19881129; DE 3852992 G DE 1988-3852992 19881129, EP 1988-311301 19881129; JP 2510264 B2 JP 1988-312775 19881210
FDT DE 3852992 G Based on EP 320164; JP 2510264 B2 Previous Publ. JP 01197502
PRAI US 1987-130889 19871210; US 1985-710929 19850312;
US 1988-236324 19880824; US 1989-361746 19890601;
US 1990-492429 19900306; US 1990-616706 19901116
REP 1.Jnl.Ref; A3...9025; GB 2151244; GB 2172295; No-SR.Pub; US 4141973; US 4582865; 01Jnl.Ref
IC A61K007-48; **C08B037-08**; C08F008-00; C08J003-24; C12P019-04; C12R001-46
ICM **C08B037-08**
ICS A61K007-00; A61K007-48; A61K031-725; A61K031-735; A61K035-12; C08F008-00; C08J003-24; C12P019-04; C12R001-46
AB EP 320164 A UPAB: 19970502

A method of obtaining a chemically modified **hyaluronic acid** (HA) preparation is claimed comprising (a) treating animal tissue containing HA with an aqs. treating mixture including an aldehyde to effect chemical modification of the HA contained in the tissue in situ, (b) removing excess treating mixture from the reaction mixture, (c) extracting the chemically modified HA from the treated animal tissue with water at below 16 deg.C and an alkaline pH of at least 8 for at least 6 hrs., (d) separating the extract cotg. the chemically modified HA from the treated animal tissue and (e) recovering the chemically modified HA from the extract.

Step (c) may be carried out with a base e.g. NaOH, KOH, NH4OH, Na2CO3, K2CO3, NEt3 or triethanolamine.The aldehyde used in step (a) may be e.g. formaldehyde, glutaraldehyde or glyoxal. The treating mixture in step (a) may include a sovlent, e.g. acetone, MEK, EtOH, isopropanol,DMF, dimethylacetamide, DMSO or CHCl3 and opt. an electrolyte, e.g. sodium acetate. The animal tissue may be rooster, chicken or hen combs which are cut into slices 1-3mm thick. Recovery may be effected in step (e) by precipitation with a quaternary ammonium cpd., pref. cetyl pyridinium chloride.

ADVANTAGE - An increased yield of hylan can be achieved in the method of GB2172295 when the temperature during extraction is kept below 16 deg.C which keeps the mol. wt.of the hylan at a high level. Higher yields are obtd. by extraction at alkaline pH. The chemically modified HA can be used in biomedical and in cosmetics, e.g. in viscosurgery, for coatings to improve the biocompatibility of various materials, as a component of various pharmaceutical prepns. or in skin care prods.. The crosslinking with **divinyl sulphone** gives a jelly-like material.

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A03-C01; A10-A; B04-C02D; B04-C03B; B12-L02; B12-M02B; D08-B09A

ABEQ DE 3645191 C UPAB: 19930923

New, chemically modified water-soluble **hyaluronic acid** prepn. contains a naturally occurring protein. It has 0.005-0.05 wt.% of aldehyde crosslinking gps. which are covalently bound to the **hyaluronic acid** polymer chain and to the protein.

USE/ADVANTAGE - The prod. has high purity. It is free from pyrogen and is non-inflammatory. It is obtd. by modifying the **hyaluronic acid** in the tissues, esp. cockscomb, before extraction. The modified prod. is then extracted e.g. with deionised water. The prod. is used for tools for surgery; for forming biocompatible coatings; as a component of pharmaceuticals and for skin care products (cosmetics). It has high elasticity, and can itself be further modified, e.g. with further crosslinking to produce water-insol. materials.

0/5

ABEQ US 5099013 A UPAB: 19930923

Chemically-modified **hyaluronic acid** prepn. is obtd. by (a) treating animal tissue with an aq. aldehyde-contg. treating mixt. to chemically modify **hyaluronic acid** content in situ. (b) removing excess treating mixt, (c) extracting the modified prod. with water at below 16 deg. C and pH 8-14 for 6 hrs. to several days.; (d) sepg. the extract from the tissue; and (e) recovering prod. from the extract.

Wt. ratio water:treated tissue is 2-5:1 w.r.t. tissue.

USE - In high yield prepn. of hylan of high mol. wt. for viscosurgery, where it protects tissues against mechanical damage, provides space and permits manipulation of tissues during surgery.

ABEQ EP 320164 B UPAB: 19950314

A method of obtaining a chemically modified **hyaluronic acid** preparation comprising: (a) treating animal tissue containing **hyaluronic acid** with an aqueous treating mixture including an aldehyde to effect chemical modification of the **hyaluronic acid** contained in the tissue, in situ, (b)

removing excess treating mixture from the reaction mixture, (c) extracting the chemically modified **hyaluronic acid** from the treated animal tissue with water at a temperature below 16 deg.C and an alkaline pH of at least 9.5 for at least 6 hours, (d) separating the extract containing the chemically modified **hyaluronic acid** from the treated animal tissue, and (e) recovering the chemically modified **hyaluronic acid** from the extract.
Dwg.0/1

L97 ANSWER 8 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1987-199004 [29] WPIX
CR 1986-118887 [18]; 1986-232217 [35]; 1987-036907 [05]; 1987-158688 [23]
DNC C1987-083237
TI Drug delivery system for slow release - comprises soluble or insol. **hyaluronan** containing drug especially in gel or cross-linked form.
DC A96 B07
IN BALAZS, E A; **LARSEN, N E**; LESHCHINER, A
PA (BIOM-N) BIOMATRIX INC
CYC 1
PI AU 8660903 A 19870604 (198729)* 38
ADT AU 8660903 A AU 1986-60903 19860805
PRAI US 1985-804178 19851129
IC A61K009-08; A61K031-40; A61K047-00
AB AU 8660903 A UPAB: 19940627
Drug delivery system comprises (a) as polymeric component, a (in)soluble **hyaluronan** or hylan; and (b) a biologically or pharmacologically active substance (I), which is controllably releasable from the system.
A soluble **hyaluronan** or hylan is used in aqueous solution for injection, use as eye drops etc., with 0.05-4 weight% of the polymer. The solution may be in the form of a viscoelastic putty. The polymer especially has a molecular weight of 1 million or higher, and (I) is typically serotonin or salicylic acid.
USE/ADVANTAGE - The polymeric component is a component of body tissues and so is safe in use. The delivery system provides for slow release of (I) in the body. When (I) contains cationic gps., ionic interaction with COOH gps. in the polymer may slow the release rate even further. The system is used for injectable, topical and other compsns.
FS CPI
FA AB; DCN
MC CPI: A03-A00A; A12-V01; B02-E; B06-D01; B10-C04B; B12-L04; B12-M10A
ABEQ US 5128326 A UPAB: 19930922
New controlled release drug delivery system comprises a polymeric insol. **hyaluronan** or sol. hylan and active agent(s), which are dissolved or dispersed in aq. soln. or viscoelastic putty hylan of M.W. 1X 10 power 6 or more. Concn. is 0.05-4(0.05-2) % wt.in water or saline at pH 7.
Drugs include serotonin, salicylic acid, and gentamycin. The hyaluran is opt. copolymerised with another hydrophilic polymer opt. with functional gp. able to react with **divinyl sulfone** e.g. a natural or synthetic polysaccharide (e.g. OHEt cellulose or glycoprotein) to which the drug is covalently bonded or held in a molecular cage. The prod. may be as polymeric porous sponge, guaze or film.
ADVANTAGE - Applicable to most drugs for most modes of admin. including eyedrops.
0/0

L97 ANSWER 9 OF 9 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1987-158688 [23] WPIX
CR 1986-118887 [18]; 1986-232217 [35]; 1987-036907 [05]; 1987-199004 [29]
DNN N1987-119110 DNC C1987-066228
TI Controlled release drug delivery system - containing soluble or crosslinked **hyaluronan** or hylan, opt. together with other hydrophilic polymer.

DC A96 B05 B07 P32 P34
IN BALAZS, E A; **LARSEN, N E**; LESCHCHINER, A; LESHCHINER, A; BAIAZS, E A
PA (BIOM-N) BIOMATRIX INC
CYC 12
PI EP 224987 A 19870610 (198723)* EN 31
R: BE CH DE FR GB IT LI NL SE
JP 62129226 A 19870611 (198729)
EP 224987 B 19920415 (199216) EN 12
R: BE CH DE FR GB IT LI NL SE
DE 3684887 G 19920521 (199222) A61K047-36
US 5128326 A 19920707 (199230) 10 A61K031-715
JP 06092320 B2 19941116 (199444) 10 A61K047-36
CA 1340199 C 19981215 (199909) A61K047-36
ADT EP 224987 A EP 1986-306046 19860805; JP 62129226 A JP 1986-219096 19860916; EP 224987 B EP 1986-306046 19860805; DE 3684887 G DE 1986-3684887 19860805, EP 1986-306046 19860805; US 5128326 A CIP of US 1984-678895 19841206, Div ex US 1984-678895 19841206, CIP of US 1985-709977 19850308, CIP of US 1985-755976 19850718, Cont of US 1985-804178 19851129, Cont of US 1988-140877 19880106, Cont of US 1989-320822 19890309, US 1990-559413 19900723; JP 06092320 B2 JP 1986-219096 19860916; CA 1340199 C CA 1986-516770 19860825
FDT DE 3684887 G Based on EP 224987; US 5128326 A CIP of US 4582865, CIP of US 4605691, CIP of US 4636524; JP 06092320 B2 Based on JP 62129226
PRAI US 1985-804178 19851129
REP A3...8746; EP 161887; GB 2172295; No-SR.Pub; US 4582865; WO 8300150
IC ICM A61K031-715; A61K047-36
ICS A61F013-00; A61K009-70; A61L015-03
AB EP 224987 A UPAB: 19940627
Drug delivery system comprises (1) as polymeric component, a soluble or insoluble **hyaluronan** or hylan and (2) a predetermined amount of at least one biologically or pharmaceutically active ingredient (I), which is controllably released at a therapeutically effective rate to a particular site.

Soluble (1) is pref. used as a 0.05-4 (especially 0.05-2) weight% aqueous solution containing (2) in dissolved or dispersed form partic. in the form of a viscoelastic putty. Insol. (1) is pref. in the form of a crosslinked gel, opt. containing at least one other hydrophilic polymer (II).

USE/ADVANTAGE - Compsns. containing soluble (1) are useful for injection of topical application as eye drops, where they remain in contact with the eye for longer, providing longer-lasting and more uniform activity. Compsns. containing insol. (1) are useful, e.g. as contraceptive devices, wound dressings, drug delivery patches, etc. Component (1) has extremely high compatibility and can be used in humans without any complications.
Dwg.0/0
FS CPI GMPI
FA AB; DCN
MC CPI: A12-V01; B02-G; B04-C02; B06-A03; B06-D01; B07-D04; B10-C04B; B12-A07; B12-K03; B12-L04; B12-M02D; B12-M10A
ABEQ DE 3684887 G UPAB: 19930922
Drug delivery system comprises (1) as polymeric component, a soluble or insoluble **hyaluronan** or hylan and (2) a predetermined amt. of at least one biologically or pharmaceutically active ingredient (I), which is controllably released at a therapeutically effective rate to a particular site.

Soluble (1) is pref. used as a 0.05-4 (esp. 0.05-2) wt.% aq. soln. containing (2) in dissolved or dispersed form partic. in the form of a viscoelastic putty. Insol. (1) is pref. in the form of a crosslinked gel, opt. contg. at least one other hydrophilic polymer (II).

USE/ADVANTAGE - Compsns. contg. soluble (1) are useful for injection of topical application as eye drops, where they remain in contact with the eye for longer, providing longer-lasting and more uniform activity.

Compsns. contg. insol. (1) are useful, e.g. as contraceptive devices, wound dressings, drug delivery patches, etc. Component (1) has extremely high compatibility and can be used in humans without any complications.

ABEQ EP 224987 B UPAB: 19930922

The use of a polymeric component as an agent for slowing the release of a substance having pharmacological activity in the prepn. of a compsn. for therapeutic treatment said polymeric component being a water-soluble or water-insoluble **hyaluronan** or hylan other than a water-insoluble cross-linked **hyaluronan** gel formed using **divinyl sulfone** as cross-linking agent. ()

ABEQ US 5128326 A UPAB: 19930922

New controlled release drug delivery system comprises a polymeric insol. **hyaluronan** or sol. hylan and active agent(s), which are dissolved or dispersed in aq. soln. or viscoelastic putty hylan of M.W. 1X 10 power 6 or more. Concn. is 0.05-4(0.05-2) % wt.in water or saline at pH 7.

Drugs include serotonin, salicylic acid, and gentamycin. The hyaluran is opt. copolymerised with another hydrophilic polymer opt. with functional gp. able to react with **divinyl sulfone** e.g. a natural or synthetic polysaccharide (e.g. OHEt cellulose or glycoprotein) to which the drug is covalently bonded or held in a molecular cage. The prod. may be as polymeric porous sponge, guaze or film.

ADVANTAGE - Applicable to most drugs for most modes of admin. including eyedrops.

0/0

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(FILE 'HOME' ENTERED AT 07:10:55 ON 03 MAY 2005)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 07:11:54 ON 03 MAY 2005
L1 1 S US20040087488/PN OR (US2003-611439# OR US2002-393220#)/AP,PRN
SEL RN

FILE 'REGISTRY' ENTERED AT 07:13:35 ON 03 MAY 2005
L2 15 S E1-E15
L3 1 S 9004-61-9
L4 1 S 77-77-0
L5 13 S L2 NOT L3,L4
L6 680 S HYALURONAN OR HYALURONIC ACID
L7 1366 S ?HYALURON?/CNS
L8 1366 S L3,L6,L7
L9 STR
L10 50 S L9
L11 3742 S L9 FUL
SAV L11 CORDERO611/A
L12 333 S 9004-61-9/CRN
L13 1368 S L8,L12
L14 1 S HYALURONIC ACID, SODIUM SALT/CN
L15 77 S 9067-32-7/CRN
L16 1368 S L13-L15
L17 5 S L11 AND L16
L18 1363 S L16 NOT L17
L19 3737 S L11 NOT L17

FILE 'HCAPLUS' ENTERED AT 07:19:35 ON 03 MAY 2005
L20 5 S L17
L21 16945 S L18
L22 16520 S HYALURONIC ACID OR HYALURONAN OR (NA OR SODIUM)()HYALURON?
L23 20380 S L21,L22
L24 2717 S L19

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L25          784 S DIVINYLSULFONE OR DIVINYLSULPHONE OR (DIVINYL OR DI VINYL)()(
L26         2924 S L24,L25
L27         6021 S HYALURONATE
L28        20802 S L23,L27
L29           36 S L26 AND L28
L30           55 S L28 AND (?VINYLSULFON? OR ?VINYLSULPHON? OR ?VINYL SULPHON? O
L31           57 S L29,L30
L32            3 S L31 AND ?INTERFERON?
                 E INTERFERON/CT
L33        67394 S E3,E32+OLD,NT,PFT,RT
L34         1244 S E32-E52
L35        66650 S E88-E113
                 E E33+ALL
L36          536 S E1,E2
                 E INTERFERON/CT
                 E E32+ALL
L37        67093 S E11+OLD,NT,PFT,RT
                 E E27
L38        66650 S E3-E28
                 E E3+ALL
L39        66951 S E6+OLD,NT
L40           39 S E8/BI
L41        82104 S E7/BI
L42            3 S L31 AND L33-L41
L43            3 S L32,L42
L44            1 S L43 AND (PARENT ? OR LARSEN ?)/AU
L45            1 S L43 AND GENZYM?/PA,CS
L46            1 S L1,L44,L45
L47            2 S L43 NOT L46
                 SEL RN

     FILE 'REGISTRY' ENTERED AT 07:29:19 ON 03 MAY 2005
L48          135 S E1-E135
L49            2 S L48 AND L17-L19
L50            1 S L48 AND 25191-25-7
L51            1 S L48 AND 26101-52-0
L52           23 S L48 AND S/ELS
L53           20 S L52 NOT L49-L51

     FILE 'HCAPLUS' ENTERED AT 07:31:34 ON 03 MAY 2005
L54          928 S L50 OR L51
L55           41 S L54 AND L28
L56            1 S L55 AND L33-L41
L57            1 S L55 AND ?INTERFERON?
L58            3 S L43-L47,L56,L57
L59            0 S L20 AND ?INTERFERON?
L60            0 S L20 AND L33-L41
L61            0 S L20 AND ?CONJUGAT?
L62            0 S L20 AND CYTOKIN?
L63            8 S L20,L58 AND L1,L20-L47,L54-L62

     FILE 'REGISTRY' ENTERED AT 07:34:16 ON 03 MAY 2005

     FILE 'HCAPLUS' ENTERED AT 07:34:37 ON 03 MAY 2005
                 SEL HIT RN L63

     FILE 'REGISTRY' ENTERED AT 07:35:13 ON 03 MAY 2005
L64           15 S E136-E150
L65            5 S L64 AND L17
L66            3 S L64 AND L16 NOT L65
L67            7 S L64 NOT L65,L66

     FILE 'WPIX' ENTERED AT 07:36:46 ON 03 MAY 2005
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L68         3943 S L22/BIX OR L27/BIX
L69         4508 S ?HYALURON?/BIX
                 E HYALURON/DCN
                 E E4+ALL
L70         2038 S E2 OR R03231/PLE
L71         1391 S E4
                 E HYALURON/CN
L72           13 S E4-E29
                 SEL SDCN
                 EDIT /SDCN DCN
L73          349 S (RAB0IN OR RA26F9 OR RA1VXB OR RA08TA OR RA08T8 OR RA121P OR
L74            2 S (RABOIN OR RAO8TA OR RAO8T8 OR RAO31D OR RAOQBE OR RAOKTS OR
L75         4793 S L68-L71,L73,L74
L76         2064 S (C08B037-08 OR C08L005-08 OR C09D105-08 OR C09J105-08)/IPC
L77         6433 S L75,L76
L78          485 S C08B037-10/IPC
L79         8422 S C08B037/IPC
L80        15620 S C08B/IPC
L81          255 S L25/BIX
L82         3702 S (?VINYLSULFON? OR ?VINYLSULPHON? OR ?VINYL SULFON? OR ?VINYL
                 E DIVINYL SULFONE/DCN
                 E E11+ALL
L83           47 S E2
L84         3710 S L81-L83
L85           58 S L84 AND L77
L86            1 S L84 AND L78
L87           49 S L84 AND L79
L88           84 S L84 AND L80
L89          127 S L85-L88
L90            4 S L89 AND ?INTERFERON?/BIX
L91            0 S L89 AND PLAFERON?/BIX
L92            4 S L89 AND (B02-V03 OR C02-V03 OR B04-H05? OR C04-H05? OR B14-G0
L93            5 S L90,L92
L94            4 S L89 AND (PARENT ? OR LARSEN ?)/AU
L95            2 S L89 AND GENZYM?/PA
L96            5 S L94,L95
L97            9 S L93,L96 AND L68-L96

     FILE 'WPIX' ENTERED AT 07:56:45 ON 03 MAY 2005

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